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ORIGINAL ARTICLES.

BRAIN TUMORS.

A Report of the Types Seen in General Practice.

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The syndrome of headache, vomiting and failing vision is indicative of increased intracranial pressure. When the history is of a progressive nature this syndrome suggests the general diagnosis of tumor of the brain. The direct measurement of intracranial pressure by lumbar puncture is somewhat difficult and, in the presence of a posterior fossa tumor with considerable pressure, may be dangerous to the welfare of the patient. Two of the most valuable procedures for detecting increased intracranial pressure are the examination of the eyegrounds and the determination of changes in the skull by means of the Roentgen ray. Evidence in roentgenograms of increased intracranial pressure is based chiefly on the number and depth of convolutional impressions, atrophy of bone about the sella and the base of the skull and separation of the sutures in children. Papilledema usually occurs early in cases of increased pressure and is sufficient evidence of the increased tension without additional confirmation by lumbar puncture. However, large noninvasive tumors which arise from the arachnoid may be present without signs of increased intracranial pressure. These tumors often grow so slowly that the flow of cerebrospinal fluid

remains unobstructed; localized intracerebral edema is uncommon and signs of pressure do not appear until the tumor has reached a large size. This type of tumor, however, often gives local evidence of its presence in the roentgenogram, as shown by an increase in the vascular channels near the lesion, calcification within the tumor or the local bone changes.[1] The slowly growing invasive tumors show the highest percentage of Roentgen signs of increased pressure, usually associated with choked disks.[2] This is also true in some cases of long-standing posterior fossa tumors which give rise to intermittent blocking of the cerebrospinal fluid pathways. The rapidly growing infiltrating tumors show a marked degree of choking of the disks but may progress so rapidly that Roentgen ray signs of increased intracranial pressure do not have time to develop.

It is important that the family doctor recognize early the complaints resulting from increased intracranial pressure or those referable to local pressure about the sella. Both young and old patients complaining of prolonged headache, or headache and failing vision, should be examined with the ophthalmoscope, the Roentgen ray and, when possible, should have studies of the fields of vision.

A thorough neurologic history and examination, including repeated perimetric tests of the fields of vision and ophthalmoscopic examinations, will usually reveal the position of the growth. The history of the onset and progression of symptoms is of great value in localization. In many cases the neurologic picture is confused by complex symptoms resulting from the marked increase in intracranial pressure. In such a patient, reduction of the pressure by the use of hypertonic solutions may be necessary in order to determine the symptoms directly referable to the tumor. In pituitary tumors constitutional manifestations may call attention to involvement in the region of the sella before signs of local pressure develop.

The Roentgen ray may be of value as an aid to localization if there is calcification within the tumor. Many meningiomata and certain gliomata tend to calcify; this calcification aids localization. It is to be remembered that intracranial calcification may be physiologic rather than evidence of tumor. Areas of physiologic calcification may be found in the choroid plexus, falx cerebri, pacchionian bodies and the pineal gland. Calcification within the pineal gland is present in over 50 per cent of the roentgenograms of normal skulls. It may be present as early as the tenth year. In some cases the displacement of the pineal shadow aids in localization of the tumor.

Pathologic intracranial calcification has been classed as either neoplastic or non-neoplastic.[3] Hematomata (Fig. 1), old abscesses, tubercles, aneurysms (Fig. 2) and areas of old meningeal disease fall into the latter class. In the neoplastic group are meningiomata, about 70 per cent of Rathke's pouch tumors (Fig. 3), certain slow-growing gliomata, hemangiomata, dermoids and cholesteatomata.

Besides the changes from general increased intracranial pressure or those from focal changes in the tumor the Roentgen ray may be of value in establishing the character, localization and extent of cerebral lesions following the replacement of cerebrospinal fluid by air. This method is frequently necessary when localization by the usual methods of examination is not definite. The replacement of the spinal fluid by air may be done by encephalography or ventriculography. Encephalography is the method of replacement of cerebrospinal fluid with air by means of lumbar or cistern puncture, in contrast to ventriculography which requires trephining the skull and introducing air by way of a cannula inserted through the opening in the skull and through the occipital lobe of the brain into the posterior horn of the lateral ventricle.

Encephalography should not be attempted in the presence of marked choking of the disks or other evidence of well-defined increased intracranial pressure. Frazier says it should not be attempted if the spinal fluid pressure is 20 mm. Hg or above, with the patient over in the horizontal lateral position.[4] In such cases the intracranial pressure should first be decreased by dehydration. This is accomplished by limitation of the total fluid intake and the addition of hypertonic solution intravenously, or by mouth or rectum. The chief indications, however, may be found in cases with obscure symptoms following trauma or inflammation, in cases of senility, in certain tumors of the brain and in cases where there are cerebral manifestations of uncertain origin. Ventriculography is used when visualization of the ventricles is desired in the presence of increased intracranial pressure, or in cases where encephalography has not been satisfactory. The procedure can be carried out under local anesthesia and is relatively safe, especially if cannulæ are placed into both ventricles so that air enters one side as the ventricular fluid is siphoned out of the other. The air should be removed after the roentgenologic studies are completed. A great deal of important information is often gained concerning the cerebrospinal fluid pathways. Although the patients complain of more or less severe headaches, fatal accidents are rare.

For purposes of diagnosis and treatment, tumors of the brain may be divided into four large groups: meningiomata, gliomata, pituitary tumors and perineurial fibroblastomata.

1. Meningiomata. Meningiomata, also known as dural endotheliomata, psammomata, meningeal or arachnoid fibroblastomata, make up about 12 per cent of tumors of the brain. They are usually slow-growing connective tissue tumors which are said to arise from the arachnoid. Recently Bailey and Bucy have described nine different histologic types of meningeal tumors.[5] They occur chiefly in the anterior fossa, especially in the region of the falx. Although they may press deeply into the brain (Fig. 4), they never infiltrate it; however, they may grow into the overlying

skull, producing exostoses. (Fig. 5, *A* and *B*.) The bony changes which are considered characteristic of these tumors are: (1) Local erosion and vascularity; (2) osteoma formation; (3) spicule formation; (4) diffuse thickening; (5) enlargement of the meningeal channels.

Calcification within the tumor itself is another common characteristic. (Fig. 6.)

A suprasellar meningioma may cause distortion of the sella, and a mistaken diagnosis of pituitary adenoma is sometimes made. It has been found in a large series that the roentgenogram reveals the presence of a meningioma in about 50 per cent of the cases.[1] In a patient with a slowly progressing history suggestive of a tumor of the brain, with or without signs of increased intracranial pressure, the presence of a meningioma is suspected. This type of tumor usually occurs in middle life. However, in the Lakeside Hospital, a large meningioma was found in a boy, aged 10 years. (Fig. 4.) Meningiomata also form a high percentage of the tumors of the brain found in psychotic patients because of the number of these tumors which affect the frontal lobes.[6]

In accessible locations the chance for surgical removal of a meningioma is very good. These tumors are very vascular, and this many times makes the operative procedure difficult. However, since the introduction of surgical endothermy into neurosurgery by Dr. Harvey Cushing, hemorrhage is more easily controlled. Deep-seated tumors may also be slowly scooped out by the electric cutting wire loop. The suspected point of origin of these tumors from the arachnoid may be cauterized, lessening the chances of recurrence. Roentgen ray therapy does not seem to hinder the growth of these tumors.

2. Gliomata. About 50 per cent of all tumors of the brain fall into the glioma group. These are the malignant infiltrating tumors which in many cases cannot be completely removed by surgical means. The diagnosis of glioma is not sufficient, however, to give insight into the probable future clinical course. Bailey and Cushing classified gliomata into over a dozen groups, and they were able to show some prognostic significance from a histologic study.[7] These groups represent certain embryologic stages in the development of the cellular types involved in the histogenesis of the brain. (Fig. 7.)

The types and relation of the tumors of the glioma group are shown in the classification starting from the neuroectoderm and developing into both adult nerve cell and into the adult glial or supporting cell.[8] Tumors arising from the germinal cells, known as medulloepitheliomata, are found as such in the roof and floor plate of the adult brain, also in the pars ciliaris retinæ. These tumors are rapidly fatal.

The majority of gliomata fall, however, into one of three groups. Of the verified gliomata in the Lakeside Hospital, about 43 per

cent are classed as astrocytomata, nearly 30 per cent as spongioblastomata and 20 per cent as medulloblastomata. The remainder are several oligodendrogliomata (Fig. 8), 1 ependymoblastoma and 1 medulloepithelioma. A certain number of gliomata vary markedly in histologic appearance in different parts of the tumor. An effort should be made with simple stains to determine the predomi-

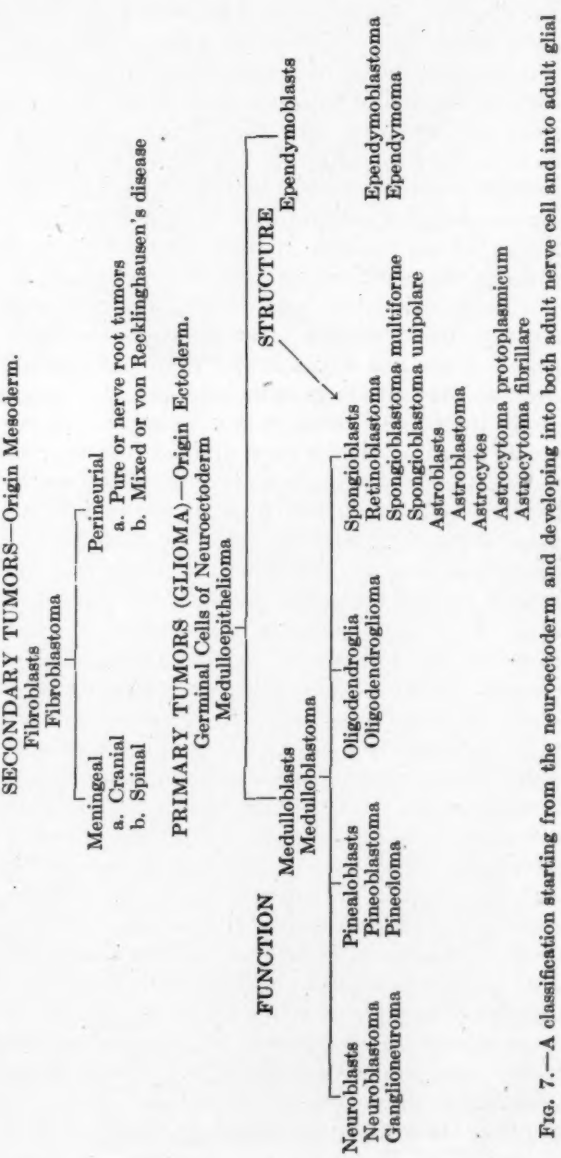

Fig. 7.—A classification starting from the neuroectoderm and developing into both adult nerve cell and into adult glial or supporting cell.

nant cell type and group it accordingly, if any prognostic significance is to be drawn from a histologic examination. The histologic picture often changes in a tumor as a result of Roentgen ray therapy or repeated surgical interference.

(*a*) *Medulloblastomata.* A medulloblastoma is a rapidly growing cellular tumor which usually occurs in the central part of the cerebellum of children. This type of tumor has been referred to as a childhood disease. Valuable time is often lost by treating chronic nausea and vomiting in children as a gastrointestinal upset before ruling out the possibility of a tumor of the brain. These tumors are composed of undifferentiated bipotential or polypotential cells which may differentiate into the various structural or nervous elements of the brain. (Fig. 9.)

Penfield[9] believes it would be better to consider that these tumors are made up of apolar (migratory) spongioblasts instead of indifferent cells, as he was unable to find neuroblasts in these tumors. With surgery the survival period of these patients is about 15 months. These primitive tumor cells, however, respond well to Roentgen ray therapy which often increases the survival period to 30 months. Roentgen ray therapy does not destroy the growth completely or prevent its growth indefinitely. Surgery should be followed by intensive Roentgen ray therapy. In cerebellar cases this consists of an erythema dose divided into four parts, given at intervals of 2 to 3 days, to alternate sides of the cerebellum. After 1 month to 6 weeks another divided erythema dose is given directly to the base of the skull with the head anteflexed.

(*b*) *Spongioblastomata.* Spongioblastomata may be divided into two groups: spongioblastoma multiforme and spongioblastoma unipolare. A spongioblastoma multiforme is characterized by multiplicity of cell forms and degenerative processes. (Fig. 10.) It is a rapidly growing cellular tumor composed of immature glial cells, chiefly bipolar spongioblasts. The usual location is in the cerebral hemispheres of adults. Cysts in these tumors are common as a result of degenerative changes and hemorrhage from poorly formed bloodvessels. Hemorrhage into the tumor probably accounts for the sudden severe neurologic symptoms which these patients often develop. This type of tumor with meningiomata forms a very high percentage of tumors in psychotic patients.[6] These tumors often run their course within a year. A spongioblastoma multiforme, as a rule, responds to Roentgen ray therapy, but not so well as a medulloblastoma. Intensive Roentgen ray therapy should always be combined with surgery.

A few tumors of the spongioblastoma group are composed chiefly of unipolar spongioblasts. (Fig. 11.) This group, known as spongioblastoma unipolare, is composed of very slow-growing tumors, often showing a tendency to calcify. They are said to respond poorly to Roentgen ray therapy. A divided erythema

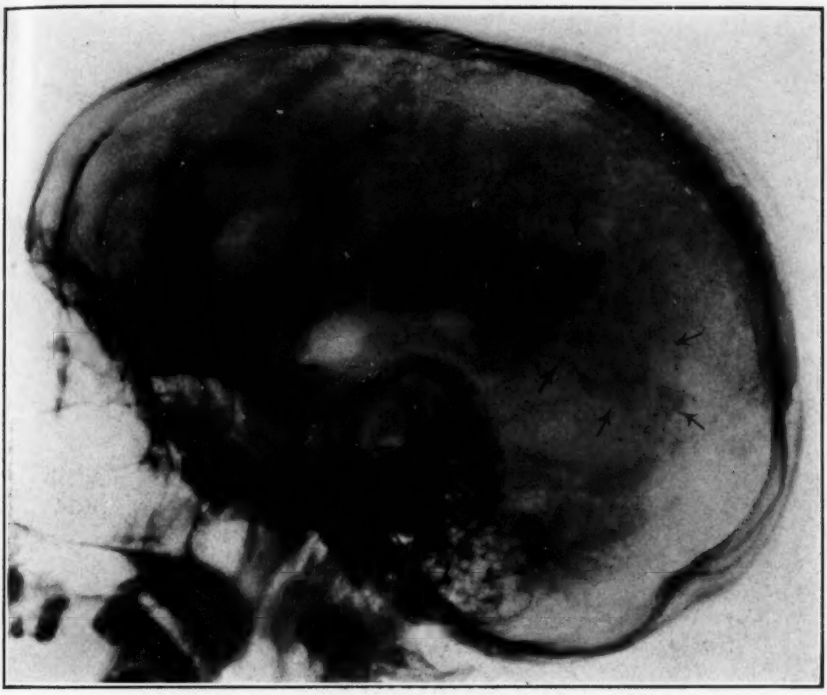

FIG. 1.—The arrows point to calcification within the brain which at exploration proved to be the result of a vascular lesion (hematoma).

FIG. 2.—Enlargement of the sella and destruction of the posterior clinoids caused by a large aneurysm of the right internal carotid artery. Note the dense linear calcification above the clivus.

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FIG. 3.—Distortion of the sella turcica and suprasellar calcification produced by a Rathke's pouch tumor. Gross tumor shown in Fig. 13.

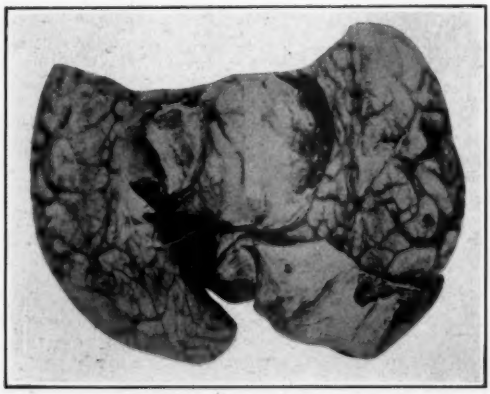
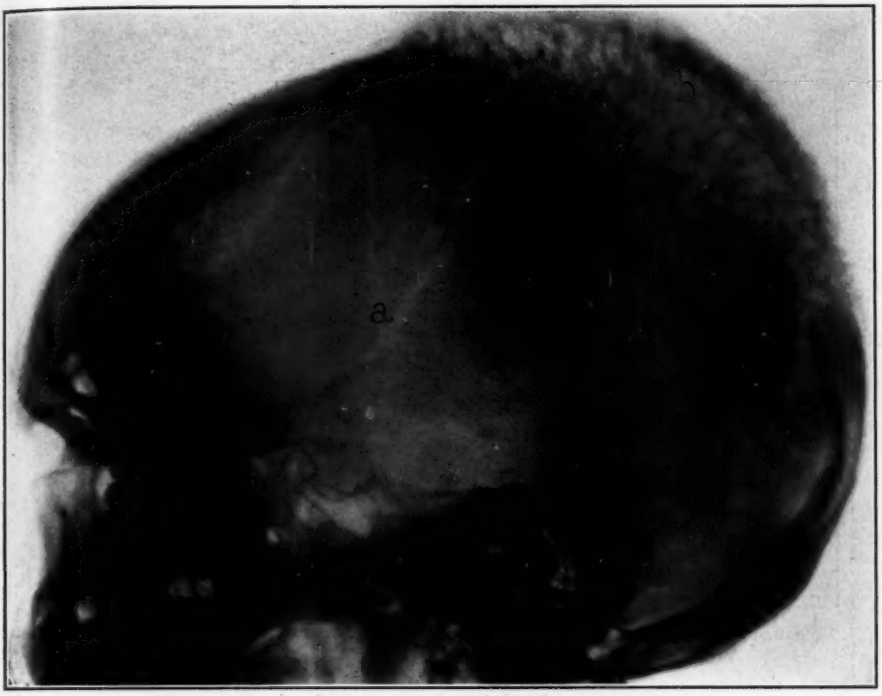


FIG. 4.—Gross specimen of a large meningioma occurring in a boy 10 years of age. The tumor was easily separated from the surrounding brain substance.



A

B

FIG. 5.—*A*. Note the prominence of vascular channels (*a*) in the region of the tumor. Meningioma infiltrating through the skull producing a large exostosis (*b*). *B*. Anterior-posterior view of Fig. 5, *A*, showing the fuzzy appearance characteristic of meningiomata infiltrating the skull.

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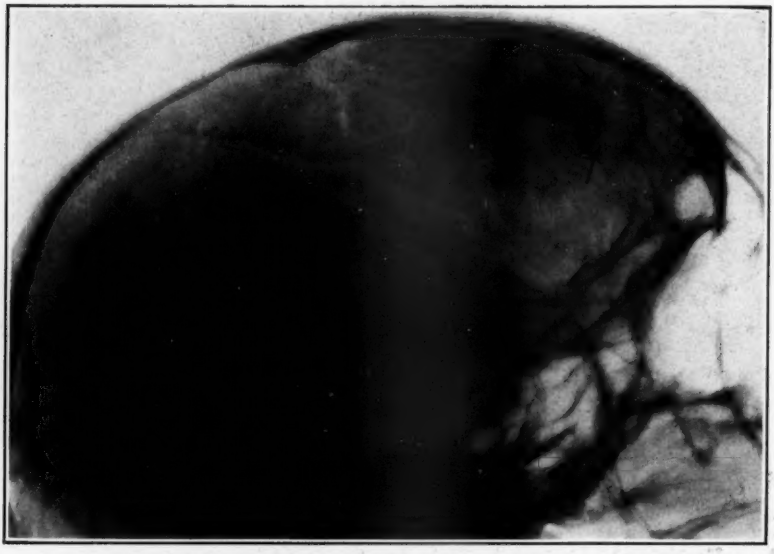

FIG. 6.—The arrows point to an area of calcification within a meningioma.

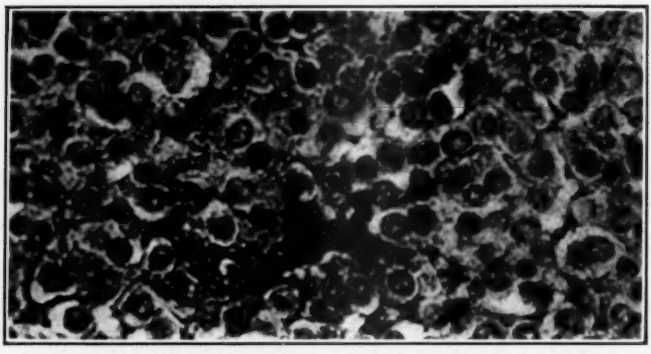

FIG. 8.—Section of an oligodendroglioma showing the spherical nuclei with a heavy chromatin network surrounded by a ring of cytoplasm which stains very feebly.

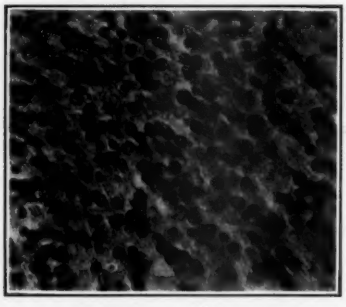

FIG. 9.—Medulloblasts infiltrating around the dark-staining granular cells of the cerebellum.

FIG. 10.—An area of degeneration in a spongioblastoma multiforme giving a "palisade" arrangement.

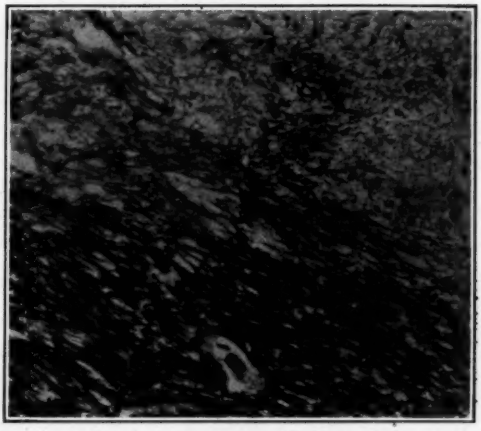

FIG. 11.—A spongioblastoma unipolare showing the wirelike cell processes of the tumor cells.

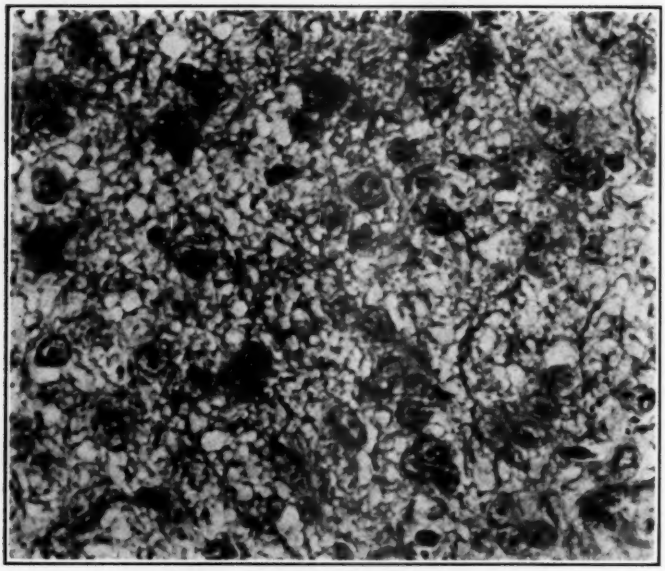

FIG. 12.—Section of a fibrillary astrocytoma showing the nuclei resting in a glial network.

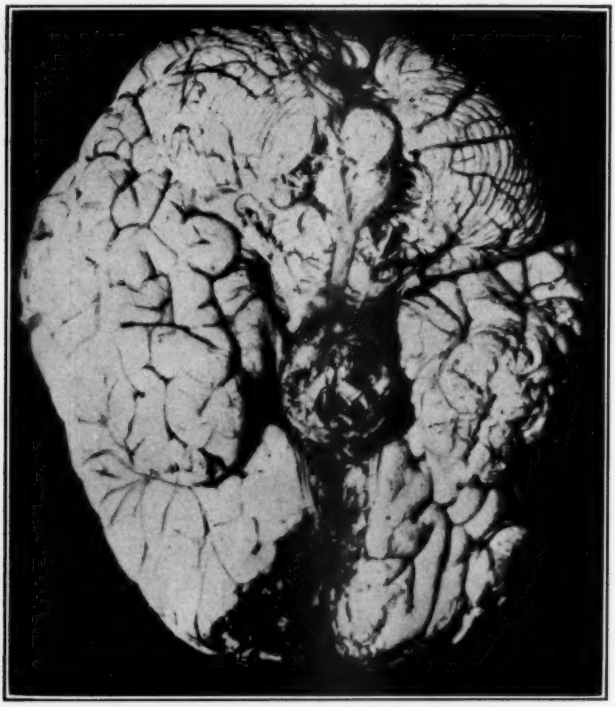

FIG. 13.—Rathke pouch tumor occurring in a young man 25 years of age.

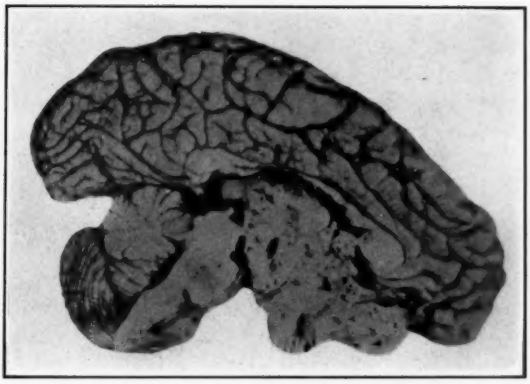

FIG. 14.—A large adamantinoma found in a girl 7 years of age.

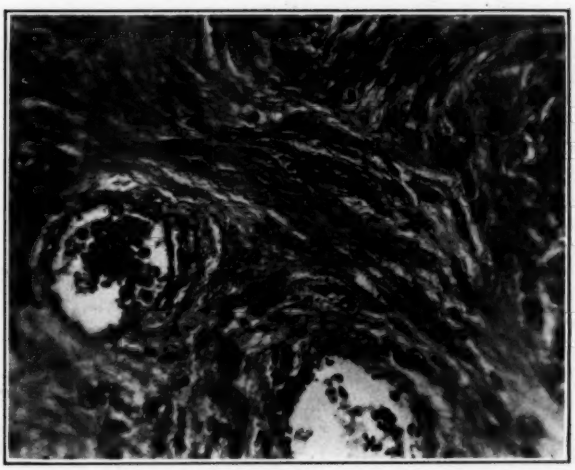

FIG. 15.—Interlacing bundles of connective tissue bands found in an acoustic perineurial fibroblastoma.

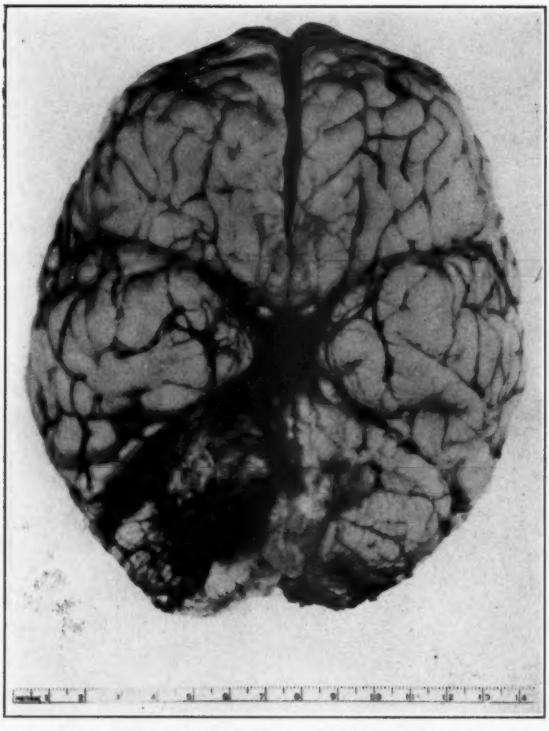

FIG. 16.—An acoustic perineurial fibroblastoma displacing the brain stem toward the opposite side.

dose of Roentgen ray directed on the tumor of each side of the head is given for a glioma of the hemisphere. The average duration of life in patients with these tumors is about 3½ to 4 years.

(*c*) *Astrocytomata.* Over 40 per cent of gliomata are composed chiefly of astroblasts or protoplasmic and fibrillary astrocytes. These two types compose the pure gliomata. Astroblastomata are only relatively benign. They compose but a small percentage of astrocytomata. Roentgen ray therapy should be used with surgery, but definite benefit is doubtful. This group has an average survival period of about 2½ years.

Protoplasmic astrocytomata are slow-growing, soft, relatively avascular tumors. These tumors may dedifferentiate and become more malignant, resembling a spongioblastoma multiforme. They are relatively benign, and the average survival of patients with this type of tumor is between 5 and 6 years. Intensive irradiation should follow surgery, for certain cases respond to this treatment.

Fibrillary astrocytomata (Fig. 12) are composed of the most highly differentiated cells. These tumors usually are found in middle life, but a certain number are found in the cerebellum of patients in the first and second decades. When exploration in these cases reveals a thick-walled cyst filled with yellow fluid a search should be made for a mural nodule of tumor.[10] This must be removed or symptoms will soon recur. These tumors are the slowest growing, the most benign and the most resistant to irradiation. The average survival period is well over 6 years. Recurrence of symptoms is usually due to refilling of a cyst or to blockage of cerebrospinal fluid circulation. It is often necessary to operate again on the cystic tumors if the mural nodule of tumor is not identified and removed at the first operation.

3. Pituitary Tumors. Pituitary adenomata compose about 70 per cent of the tumors occurring in the region of the sella and about 5 per cent of all tumors of the brain. They may be composed chiefly of neutrophilic (also called chromophobe), acidophilic or basophilic cells. The two well-known varieties of pituitary adenomata composed of chromophil or chromophobe cells have definite constitutional manifestations apart from the local or pressure effects of the tumor which may call for surgical relief. Chromophobe adenomata may be associated with hypopituitarism, while the chromophil adenomata accompany the syndrome of acromegaly or hyperpituitarism. In the Lakeside Hospital a basophilic adenoma has been found in a polyglandular patient in whom the secondary sex characteristics were overdeveloped.[10a] Frazier[11] has recently advocated glandular feedings of pituitary and thyroid extract for pituitary dysfunction without pressure phenomena. About 80 per cent of pituitary adenomata are solid, while the remaining 20 per cent are cystic. Formerly surgery was advocated in all cases of pituitary tumor with symptoms of increased intracranial pressure,

also with symptoms due to local pressure, such as blindness, oculomotor palsy, pituitary headache and in cases of acromegaly. At the present time surgical intervention is resorted to when vision is threatened or the headaches are very severe.

Recently good results have been reported by Towne from Roentgen therapy when used for suspected solid adenomata of the anterior lobe which have enlarged or destroyed the sella.[12] These treatments are to be followed closely by perimetric examinations. Roentgen ray treatments may be safely tried 6 months before surgery if there is no loss in the visual fields. Relief is usually not obtained under 6 weeks to several months. A cystic tumor is suspected in cases which do not respond to Roentgen ray therapy and these must be treated surgically. At the Lakeside Hospital a divided erythema dose of Roentgen ray is given to each side of the head, directed upon the sella. Some advocate intensive treatment to the front, top and back of the head in addition to the above method.

Nearly 20 per cent of tumors about the sella are craniopharyngeal pouch or Rathke's pouch tumors. (Fig. 13.) From such pharyngeal rests most unusual forms of neoplasm infrequently develop such as adamantinoma. (Fig. 14.) These congenital tumors arise from the pharyngeal pouch which forms the anterior lobe of the pituitary gland. They usually occur within the first or second decade of life. In young patients a picture of dyspituitarism is usually seen, consisting of nondevelopment of the sexual organs, dwarfism and a lowered basal metabolic rate. Mentally the patients are alert and even precocious. About 70 per cent show suprasellar calcification by Roentgen ray.[13] (Fig. 3.) Treatment consists of aspirating the cyst by a transfrontal approach to save eyesight. These tumors do not respond to Roentgen ray therapy.

4. Perineurial Fibroblastomata. These tumors are also known as acoustic neuromata, or spinal nerve tumors, and are said to compose about 6 per cent of all tumors of the brain.[14] The patients usually give such a classic history that the correct diagnosis can be made in about 90 per cent of the cases. The Roentgen ray gives additional confirmation in a few cases. The pure perineurial fibroblastomata arise from the perineurium or endoneurium surrounding the nerve fasciculi.[15] (Fig. 15.) They are usually attached to the cranial or spinal nerve roots. (Fig. 16.) In the cranial group the left acoustic nerve for some unknown reason is most often involved. The first and fifth cranial nerve roots are the next most common sites for these tumors. The nerve fibers are found passing around these tumors and not through them. In von Recklinghausen's neurofibromatosis bilateral involvement of the vestibular portion of the eighth nerve is not uncommon. In certain cases this may be the only manifestation of the disease. The histologic picture varies from that of the pure perineurial fibroblastoma. Nerve fibers pass through the tumor in von Reckling-

hausen's disease, but local areas may be found in these tumors identical with perineurial fibroblastomata. These tumors are very slow growing and do not respond to Roentgen ray therapy. They are in a difficult place to obtain exposure sufficient for complete removal. Again electrosurgery has made it possible to remove more of these tumors with greater ease and safety through the suboccipital approach. Surgery usually prolongs the life of these patients from 3 to 6 years, and in many cases the tumor may be completely removed.

Conclusions. There are several reasons for surgical intervention in cases of tumor of the brain. Regardless of the pre-operative pathologic diagnosis, exploration may reveal a lesion which is amenable to radical surgical treatment. Lesions which are amenable to surgery are meningiomata, certain acoustic neuromata and astrocytomata. At operation it is hoped to confirm the presence of a tumor and more accurately to localize it. If a specimen for histologic study is obtained the future course of the patient will be better understood and Roentgen ray therapy can be more accurately given. The prognosis in patients with gliomata can be made fairly accurately as to time and subsequent course only by histologic study. A decompression is usually done at the time of the exploration and this provides a safety valve which will take care of a reactionary edema or even hemorrhage into the tumor resulting from Roentgen ray therapy.

Roentgen ray therapy should be combined with surgery in the treatment of gliomata. The more embryonic the predominate type of cell in the tumor, the more effective this form of treatment will be. Cystic tumors of the pituitary should be treated surgically, while many solid adenomata of the anterior lobe of the pituitary may be controlled by Roentgen ray therapy alone.

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ENDOCRINE THERAPY IN THE PSYCHOSES.*

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The psychoses presents a problem in medicine, the magnitude of which is commonly much underestimated. In 1930 the average number of occupied hospital beds in the United States was about 736,000. Of these, well over half, or about 419,000, were occupied by victims of nervous and mental disorders. Of these, in turn, the the great majority were frankly psychotic. Schizophrenia, or dementia præcox, alone furnished the occupants for one-fifth of all occupied beds. The economic cost of the disorder in this country is well over $1,000,000 a day. The social cost cannot be calculated: The disorder characteristically takes onset in the early prime of life and runs through a life span that is not greatly shortened; each case represents a wrecked life and a grave social maladjustment. This psychosis, then, presents the outstanding medical problem of today. Since it has been most adequately studied, this discussion will deal primarily with schizophrenia, but with incidental attention to some of the other psychoses.

Whether schizophrenia is fundamentally of psychogenic or of organic origin has been long and rather unprofitably debated. That emotional stresses play a large part in precipitating the disorder cannot be questioned. The burden of the evidence, however, indicates rather conclusively that it is dependent also upon a constitutional liability factor. It shows a predilection for individuals with tainted heredity and of dysplastic constitutional types. The most convincing datum is the high incidence of double involvement in monozygotic as compared with ordinary fraternal twins.[1] These characteristics are most plausibly explicable on the assumption that the disorder arises only in those organically liable to it.

Much thought and more than a little research have gone into an attempt to identify the underlying liability factor or factors. A large body of respectable opinion holds that the subjects are victims of some sort of vague metabolic disorder amounting to a chronic intoxication. This, in turn, might well depend directly or indirectly upon abnormal endocrine functions.

The question arises whether, as a matter of fact, endocrine abnormalities can be demonstrated as a common factor in the psychosis.

* Read before the Division of Medical Chemistry, American Chemical Society, Buffalo, September 3, 1931.

If not, endocrine therapy would presumably offer little hope. Three lines of evidence in this connection demand consideration. Is there a significantly high incidence among schizophrenics of the morphologic stigmata of endocrine abnormalities? Are the physiologic and metabolic functions distorted as they are in endocrine disorders? Do the endocrine glands of the psychotic subjects themselves show characteristic pathologic changes?

Morphologic Stigmata. Wertham[2] has recently reported a study of bodily abnormalities in 923 unselected psychiatric patients. He considered skeletal abnormalities, lack of symmetry, bodily disproportions and malformations, anomalies of primary and secondary sex characteristics, of fat distribution, of hair distribution and complexion. More than a third of his schizophrenic group showed such disorders. A similar high incidence of constitutional abnormalities has been reported by Raphael, Ferguson and Searle,[3] by Schmidt[4] and by Kretschmer.[5] Abnormalities in the sex field are especially common in schizophrenia as they are in demonstrated endocrine dysfunctions. Too, there is a high incidence of the so-called "thymolymphatic constitution," a condition marked by scanty beard, axillary and sternal hair; slender thorax; rounded contour of the upper arms and thighs; genital hypoplasia and velvety skin. These constitutional deviations are interpreted by most students as due primarily to glandular abnormalities. The outstanding evidence was reviewed by Hoskins[6] in 1929.

Physiologic and Metabolic Disturbances. Perhaps the most characteristic single finding in endocrine deficiency is depression of the basal metabolic rate. There are now available in the literature reports on approximately 300 cases of schizophrenia that include data on this topic (Fischer[7] and Hoskins and Sleeper[8]). These reports sufficiently demonstrate that the disorder is characterized by a systematic depression of over 10 per cent. Fischer has noted, too, a characteristic depression of the specific dynamic action of food, suggesting to him pituitary deficiency as the outstanding etiologic factor. These depressions are commonly noted in patients in whom no intercurrent physical disorders can be detected to account for the deviations and constitute substantial presumptive evidence of endocrine deficiency. The sugar metabolism likewise is rather commonly abnormal. The literature on this point was reviewed by the authors in 1930.[9] The blood pressure is depressed on the average about 10 per cent. The literature on this point has recently been compiled by Freeman, Hoskins and Sleeper,[10] who have added studies on 180 cases. The disorder is characterized by a great variety of other perturbations throughout the domain of the autonomic nervous system. These include cyanosis of the extremities, dermographism, inequality and irregularities of the pupils and sweating. Low body temperature and fatigability are likewise common findings.

On the whole, the metabolic and functional characteristics of the psychosis are strongly suggestive of endocrine deficiencies. Granted technical competence the metabolic deviations could probably all be reproduced by creating suitable glandular abnormalities. On the other hand, the defects might conceivably be accounted for, in part, at least, by chronic emotional disturbances.

Endocrine Pathology. There is a fairly large body of literature indicating a high incidence of structural defects in the endocrine glands in case of schizophrenia and to a less extent in case of other psychoses. Deficiencies in the sex glands are especially frequently reported. Cushing[11] has stated that he failed to find a single normal pituitary in 70 State Hospital cases. Abnormal thyroids, too, have been frequently reported, regressive signs being especially common. On the whole, it may be said that fairly extensive changes, generally of a degenerative nature, are commonly found in the endocrine glands of the schizophrenics. Whether, however, these changes are characteristic of the psychosis as such, or whether they are incidental to age, or to the intercurrent diseases or nutritional state of the patients, the existing evidence fails to prove. As a matter of fact, there are practically no studies in the literature based on adequate cytologic technique and with suitable control material. Until such studies are made in sufficient number to permit valid statistical analysis we shall presumably remain in the dark as to whether structural endocrine abnormalities are a consistent part of the picture.

Personality Changes and Gland Defects. Direct evidence that endocrine deficiencies can produce striking personality deviations can be cited in considerable amount. McLester[12] has described a clinical picture of general "poor health" due to thyroid deficiency and marked by chronic nervous exhaustion, impairment of the reasoning power, incapacity for mental effort and lack of initiative. Such patients are definitely benefited by thyroid treatment. Wagner-Jauregg[13] recognizes a prepsychotic type of personality associated with hypoplastic constitution due to combined ovarian and thyroid deficiency. This type is likely to develop hebephrenia, but may go through life merely showing futile personality. In either case, the author believes combined thyroid-gonad medication to be beneficial. Schrijver-Hertzerga and Schrijver[14] reported a notably careful study of a peculiar case of "degenerative psychosis" with schizoid, cyclothymic and hysteric features and periodic attacks of confusion. In the features of late maturity, obesity, sterility and various metabolic findings the physical status suggested thyroid deficiency. Prolonged study proved the unequivocal beneficial effect of thyroid medication. It is a matter of textbook knowledge that high grades of thyroid deficiency result in general sluggishness, dulling of the sensibility, retardation of thinking as well as motor activity. The mood is not infrequently depressed, and in severe

cases illusions and hallucinations of hearing, sight, smell and taste and even compulsive states occur. Lawrence and Rowe[15] have specifically recognized another variety of hypothyroidism, "the thin, irritable type," in which the subjects, far from being sluggish, are pathologically overresponsive to environmental annoyances. These patients promptly normalize under thyroid medication. Santenoise[16] has published voluminous experimental evidence that cerebral functions are markedly affected by variations in the amount of thyroid hormone in the circulation.

That the gonads play an important rôle in determining personality has been believed from time immemorial. Castration is commonly regarded as calamitous. Certainly in the lower animals, and probably often in man, deprivation of the testicular secretion results in a loss of those characteristics connoted by the term virile. Ovarian deficiency of women often results in fatigue, general weakness, headache, irritability and depression. In Rowe's[17] graphic terms, "an insistently expressed egoism is the keynote of the hypogonad character. Coupled with and dependent on this is an active resentment toward a world that is but inadequately mindful of the patient's many excellencies. Hyperemotionalism and self-pity are united with an attitude of acrid criticism of environmental conditions that are always unsatisfactory. The psychologic study of the average woman suffering from ovarian insufficiency would be a profitable but scarcely a pleasant task." The occasional occurrence of profound melancholia at the climacteric period in both men and women is another datum suggestive of the importance of the gonad secretions in maintaining normal psychic life.

The recent demonstration of the determining influence of the anterior lobe of the pituitary on the sex functions suggests that this gland, too, may be involved in the aforementioned manifestations of gonad deficiency. The administration of the sex-stimulating fraction of anterior pituitary extracts has definitely been shown to exercise an erotizing effect in immature or castrated animals. Tucker[18] has described a condition of "pituitary psychosis" that in his opinion derives from deficient secretion of this gland and can be ameliorated by pituitary medication. The psychosis resembles dementia præcox but marked hysteria may also be evident.

The parathyroids, too, are well known to have an important influence on nervous activities. Parathyroid deficiency has often been shown to result in tenseness that may extend even to clonic convulsions. Clouding of consciousness is occasionally noted and a considerable number of outspoken psychoses have been reported with hallucinatory confusion and mood disturbances. In chronic parathyroid tetany mental dullness and enfeeblement are not uncommon. Looney[19] has reported some success in the control of the rigidity of catatonic dementia præcox patients by the use of parathyroid extracts. Bowman[20] and the present writers have

failed to demonstrate any very significant clinical effects from such medication. Timme[21] has recognized a peculiar behavior disorder that is apparently correlated with parathyroid deficiency. The patients showed incorrigibility, unamenability to discipline and assaultiveness. A trifling provocation sufficed to arouse intense anger. In several instances the condition progressed to a hypomania that demanded institutional treatment. Under parathyroid extract supplemented by calcium and sunlight the tenseness, myotatic irritability and conduct disorders rapidly improved.

That other endocrine organs have more or less definite influence on the higher nervous functions is altogether probable, but the unequivocal evidence is too scanty to warrant more than casual mention. Pineal tumors are at times associated with mental as well as physical precocity. Deficiency of the thymus has been reported as common in mentally deficient children. The general lassitude characteristic of adrenal deficiency no doubt repercusses significantly in the mental sphere. The terminal delirium of Addison's disease demonstrates a relationship if only secondarily and as an expression of toxemia.

Altogether, there can be no doubt that endocrine deficiencies play an important part in determining the functional capacity of the higher nervous system. The probability that the psychoses are significantly correlated with such deficiencies accordingly possesses a probability little short of certainty. There can be no doubt, then, that the problem of the psychoses justifies an exhaustive experimental endocrine therapeutic approach. Ideally, however, gland therapy should be prescribed only for patients in whom adequate diagnostic studies have disclosed specific indications. It is not surprising that in view of the well-known lag in the development of diagnostic methodology in this field a great deal of random endocrine therapy has been practised.

As would be expected under such circumstances, numerous failures have resulted among psychotic as they have among nonpsychotic patients. More than 20 years ago Kraepelin[22] wrote: "Many years ago I endeavored to acquire influence on dementia præcox by the introduction of every possible organ, of the thyroid gland, of the testes, of the ovaries, and so on, unfortunately without any effect." In this, as in all similar cases, however, the question still remains open. Negative evidence is conclusive only when it is shown that a preparation of the gland appropriate for the individual patient was selected, that a potent product was used, that the dosage was adequate and that the treatment was continued for a sufficient period. We know of few reports of negative results in which these criteria have been met.

Until recently, therapeutists have been sadly handicapped by the lack of potent gland preparations. Such hope as there may be in the endocrine treatment of the psychoses has been and is being

rapidly improved by successful world-wide researches on the chemistry and pharmacology of the glands.

Endocrine Therapy. In the actual successful endocrine treatment of psychotics the palm would seem to go to Lewis and Davies.[23] From the wards of St. Elizabeth's Hospital they selected for treatment 20 schizophrenics, and in all cases definite physical or mental improvement, concurred in by 6 observers, was obtained. Four made sufficient mental improvement to be discharged and 9 others partly recovered.

Kauders[24] has reported a study on the efficacy of male and female gonad extracts. He concludes that treatment must be extended over months and that from 15 to 20 times the usual indicated dosage must be used. He reports specifically on the treatment of 8 male schizophrenics who had been getting progressively worse for years. One paranoid and 1 catatonic subject showed noticeable improvement after the first 3 weeks, 1 finally being completely cured. One subject, for 2 years in stupor, after the third month's treatment showed no psychotic symptoms except negativism. Another, paranoid, for 3 years, corrected his delusions after 3 months' treatment and showed general improvement. The other 4 patients had shown no mental improvement, but 2 were improving physically. Similarly favorable results from testis extracts, especially in cases of early onset, have been reported by Keresztes.[25] Sippel[26] has reported uniformly successful results in 6 patients into whom healthy ovarian tissue was transplanted. Bentley[27] reported strikingly favorable results in chronic cases following the administration of a mixture of thyroid, gonad and pituitary substance.

Mayer[28] reported the case of a rather typical catatonic who, under thyroid treatment, went through a manic phase, then became free from mental symptoms. Davidson[29] also reported a single case successfully treated with thyroid substance in increasing doses up to 60 grains daily.

Hübner reported good results from thyroid medication in a few cases, but since he noted an equally favorable influence from antithyreoidin his evidence is equivocal. Sawkins[31] reported an illustrative single case of a man, past 50 years of age, a hospital inmate for 20 years; he was an idle, pestilential, petty thief and fomenter of discord, who spent most of his time in the refractory ward. After reaching 75 grains a day (probably in terms of fresh gland) the thyroid was gradually reduced to 5 grains. In the latter stage of the treatment the patient's weight and vitality increased, his conversation became sensible and in a few months he became notably trustworthy. He was ultimately discharged and for the past few years had been self-sustaining.

During the current year Hayward and Woods[32] have again emphasized the importance of thyroid deficiency as a factor in the malfunctioning of the brain cells. Their experience coincides with

that of previous authors in showing that thyroid deficiency may result in either a depressed psychosis or in irritability and excitement leading to the diagnosis of mania. The patients may show thought distortion with hallucinations and delusions which may become so bizarre as to be interpreted as signs of dementia præcox. They reported a case of frank psychosis with schizoid coloring in a woman, aged 41 years, who showed various metabolic evidences of thyroid deficiency. Under thyroid medication the psychosis completely cleared up.

For the past 4 years we have been engaged in a somewhat elaborate diagnostic and therapeutic investigation of the schizophrenia problem at the Worcester State Hospital. So many are the variables in the problem, however, and so difficult is adequate control that few final conclusions are yet possible.

The characteristic metabolic picture in schizophrenia is strongly suggestive of suprarenal cortex deficiency as a common underlying feature. With the suprarenal preparations, however, that have been available to us no significant amelioration of the psychosis—nor, indeed, any significant influence on the metabolic functions—have been recognized. A study on 9 cases has recently been reported.[33] Similarly, we have obtained negative results with a glycerin extract of bovine testes. The results with pituitary preparations have been equivocal, but there is a suggestion of a beneficial effect that demands a careful statistical analysis of our data.

Last year we reported a "first approximation" of results secured with thyroid therapy.[34] Among 130 subjects of dementia præcox a group of 18 was diagnosed as suffering from thyroid deficiency. Of these, 16 received thyroid treatment. Significant mental improvement followed in 14, or 88 per cent, of the cases, and 5 patients had become well enough to go home. A control group of 41 patients in whom definite thyroid deficiency could not be recognized but who had received similar thyroid treatment was available. The incidence of significant improvement in this group was only 34 per cent. Since 31 of the group were recorded as showing "endocrine deficiency unclassified," it is probable that some of these subjects, too, suffered from some degree of thyroid deficiency, a fact that may account for some of the improvement noted. Also, a considerable number of the control subjects had received other types of medication and this, too, may have contributed somewhat to the improvement. Here, as in all cases, however, a troublesome factor, namely, "spontaneous variability," no doubt intruded. The contrast between 88 per cent of hypothyroid patients showing improvement under this medication with 34 per cent of the control group not demonstrably hypothyroid was offered as evidence of a specific therapeutic effect. Since the series was made up almost entirely of cases having an ominous prognosis, the beneficial effects seemed to possess an added significance. The results were interpreted as indicating that thyroid deficiency plays a significant rôle in more

than 10 per cent of hospitalized cases of dementia præcox, and that in properly selected cases thyroid medication in adequate dosage and for a sufficiently prolonged period results in significant improvement. On the other hand, relatively little success is to be anticipated from thyroid medication in cases selected at random. A striking feature of our data is an indication that the threshold for thyroid medication in this disorder is frequently surprisingly high, and that relatively very large doses can be safely administered or, indeed, must be administered to secure significant therapeutic results. Further studies since the publication of the data reported suggest that upon discontinuance of the thyroid therapy the improvement is likely to be lost. Likewise, there is a suggestion that there are often other etiologic factors operative even in the hypothyroid subjects and that these, too, must be corrected before complete success can be achieved. No final conclusions can be drawn until many more studies have been made and the data subjected to rigid statistical analysis to determine the relative weights of the presumably numerous factors involved in the equation.

A major difficulty in such studies is the looseness of the term schizophrenia itself. It is not unlikely that the disorder comprises a variety of distinct affections just as the term fever may denote pneumonia, arthritis, starvation, dehydration or what not. Before finally conclusive results can be anticipated in either diagnostic or therapeutic studies it will probably be necessary to determine much more specifically the component varieties of the psychosis.

Summary. It may be said that in all probability the psychoses are influenced in a variety of ways by the endocrine status of the subjects. There is abundant justification for elaborate and long-continued diagnostic and therapeutic studies of the significance of endocrine factors. Successful results from endocrine medication in a variety of cases have been reported, but, in general, control studies have been inadequate or totally lacking. The importance of the psychoses among the acute medical problems of the day has been commonly underestimated. Research in psychiatry now lags far behind that in organic medicine. The number of hospitalized cases of different disorders can be taken as a rough indicator of the need for research in each. If this be granted, it must be conceded that not until the mental and nervous disorders are receiving as much attention as all other diseases combined will a proportionately fair allocation of effort have been achieved.

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WHITE BLOOD CELL COUNTS IN CONVALESCENCE FROM INFECTIOUS DISEASES.*

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The Schilling[1] hemogram is of distinct value in a study of acute infections. It is probably the most delicate index of severity of illness, prognosis and imminence of complications which the laboratory can offer.[2] However, the help of the laboratory, as far as blood counts are concerned, is frequently just added information. The clinician, as a rule, can tell when a patient is acutely ill. In a typical acute infection like lobar pneumonia the appearance and complaints of the subject, the physical signs which can be elicited, and the temperature, pulse and respirations offer a definite picture which indicates that a person is sick. It is much more difficult to determine when a patient is well, and it is during recovery and convalescence that the hemogram can be of decided help. Most physicians and hospitals have a routine in gauging convalescence. In acute lobar pneumonia a patient is usually permitted to leave his bed after his temperature has been normal for 10 days. After an attack of grippe many patients are no longer confined to bed after four days of normal temperature. In such diseases as acute rheumatic fever bed care is much more variable, but judging from the frequency of complications and recurrences no definite idea is prevalent among physicians as to when the phase of convalescence has ended and that of recovery begun. Swift[3] emphasizes the need for convalescent care in rheumatic fever long after the symptoms and signs of the acute disease have disappeared. This indicates how unreliable the patients' symptoms and signs are in this condition as evidence of recovery.

It is obvious that no two patients are alike in illness or in recovery from illness and that a blanket rule of a given number of days of convalescent bed care may be insufficient for some patients and too much for others. It is a common experience that a certain number of patients feel in excellent condition after leaving their beds and others, after an apparently similar illness and similar convalescent course, feel decidedly below par.

* This report was made possible through the courtesy of Prof. Victor Schilling, under whose direction the author worked for part of this study.

This investigation was supported in part by the Committee for the Encouragement of Medical Research.

At the suggestion of Prof. Victor Schilling, a study was undertaken to see if, in patients suffering from various acute infections, some information could be obtained from the hemogram or Schilling index as to the progress of convalescence.

The technique used was similar to that employed in the previous study of the acute phase of infectious diseases.[2] Total white blood cell counts were made with standardized pipettes, as far as possible under Garrey's[4] basal conditions at regular intervals. The Schilling counts were made from coverslips, stained with Wright's stain and prepared at the same time that the blood was drawn for white cell counts. Table 1 illustrates the values considered normal for the different cells in this work. Basophils are not given because they play no important part in this study. Between 6000 and 8000 is called a normal total count. Both percentages and absolute values were determined, but the latter were found to be of much less value than the percentage determinations because of the great variation of total count in different phases of pathologic conditions.

TABLE 1.—NORMAL VALUES OF CELLS (BASED ON ABOUT 250 CASES).

	Per cent.	Total count. per. cu. mm.
Immature polymorphonuclears:		
Myelocytes		
Young forms		
Band forms	4–7	240–560
Mature polymorphonuclears	50–65	3000–5200
Lymphocytes	20–38[5]	1200–3000
Monocytes	3–10	180–800
Eosinophils	0.5–3	30–240

About 200 patients were studied, a few on the wards of the First Medical Clinic of the Charitékrankenhaus, Berlin, and most on the wards and in the out-patient department of the Second Medical Division of Bellevue Hospital. The diseases followed were: pneumonia, rheumatic fever, infectious arthritis, acute tonsillitis, scarlet fever, erysipelas, cerebrospinal meningitis and lymphangitis.

All these patients showed minor variations in their counts, especially in the degree and duration of the rise of certain forms. Also various diseases presented somewhat different patterns. But in general, convalescence from all the infections studied produced hemograms which were remarkably constant.

During the active infection the hemogram shows an increase in immature polymorphonuclear cells ("shift to the left"), and a depression of lymphocytes, monocytes and eosinophils. These changes are both relative and absolute. As the intensity of the infection subsides there is a decrease in the number of immature polymorphonuclear cells and the monocytes increase abruptly. In some conditions like pneumonia this increase in monocytes may last a very short time, sometimes for only 24 hours. As convalescence progresses the immature polymorphonuclears return to normal, the monocytes decrease and the lymphocytes and eosinophils

increase. Complete recovery is usually accompanied by a return of the hemogram to normal.

There are many variations of this process. In some infections, such as infectious arthritis, the high monocyte phase may last a long time. In diseases like rheumatic fever, scarlet fever, tonsillitis and in a few patients with pneumonia the eosinophilic increase (from 5 to 17 per cent) may occur early in convalescence and recur late in convalescence or may persist a long time. The duration of the high lymphocyte count may vary markedly in individual cases. Moreover the various phases may overlap.

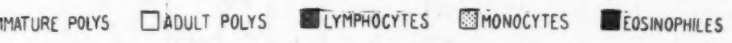

CHART I.—Designation of various white blood cells in charts.

To obtain a clearer view of the hemogram in convalescence a few cases may be selected as illustrations. In the charts to be presented Chart I illustrates the manner of designating the various cells: Solid black represents immature polymorphonuclears; clear area, adult polymorphonuclears; diagonally lined, lymphocytes; stippled area, monocytes; horizontally lined, eosinophils. As mentioned previously, basophils were not included because they have no importance in this study. In some of the tables the total values are included as well as percentages, but as will be demonstrated in one of the charts (Chart V), the striking features of this study are evident, regardless of whether percentages or total counts are used.

In the first place, Chart II and the accompanying Table II show the course of hematologic events in an acute infection with fatal outcome.

Case Abstracts. CASE 1.—This patient (J. O'B.), in brief, was a male, aged 37 years, admitted with a history of a cough for 4 weeks and a sudden chill, cough and generalized pains 3 days before admission. His left upper lobe showed classical signs of consolidation and he died 6 days after his admission.

The chart shows that on admission his temperature was 105° F., and he had a marked increase in his immature polymorphonuclear cells (54 per cent), with a depression of his lymphocytes and monocytes (3 and 6 per cent respectively) and an absence of eosinophils. His condition improved in the next 3 days so that his temperature dropped to 101° F., his immature polymorphonuclears declined and there was a slight rise of his lymphocytes and a marked rise of his monocytes (18 per cent on January 13). But 2 days before his death (and the day before to a marked extent) there was a definite increase in his immature polymorphonuclears. On the day he died his immature polymorphonuclears numbered 67 per cent and his lymphocytes and monocytes were markedly depressed (4 per cent each), with a complete absence of eosinophils.

This case, therefore, illustrates the cardinal features of bad prognosis as far as the hemogram is concerned: increase of immature polymorphonuclears, decrease of lymphocytes, monocytes and absence or marked depression of eosinophils.

With this case in mind it may be of interest to study the results obtained in an individual who recovered from an attack of lobar pneumonia.

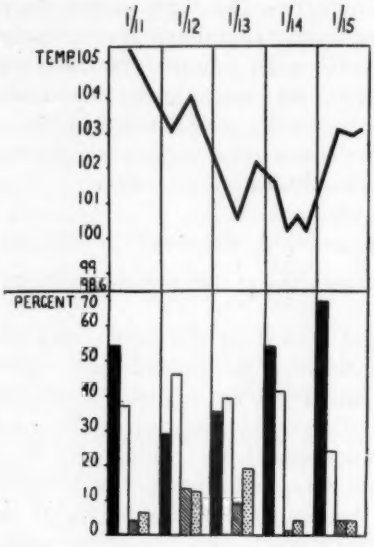

CHART II.—Hemogram of patient J. O'B., who died from lobar pneumonia.

TABLE 2.—HEMOGRAM OF CASE 1; DIED FROM LOBAR PNEUMONIA.*

Date.	W.B.C.	Immature polys.		Adult polys.		Lympho-cytes.		Monocytes.		Eosinophils.	
		Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.
1929											
Jan. 11 . .	7.5	54	4.1	37	2.8	3	.225	6	.450	0	0
12 . .	7.0	29	2.0	46	3.2	13	.900	12	.850	0	0
13 . .	7.6	35	2.7	39	2.9	8	.600	18	1.350	0	0
14 . .	11.0	54	5.9	41	4.5	1	.100	4	.450	0	0
15 . .	10.1	67	6.8	24	2.4	4	.400	4	.400	0	0

* In this and subsequent tables all white cell counts are recorded in thousands per cu. mm.

CASE 2.—The patient (S. K.), represented by Chart III and the accompanying Table 3, was admitted with the history of having had a chill 3 days before admission, complaining of general aches, nausea, vomiting, slight productive cough and having slight pain in his upper chest. Upon examination he had some polypnea, slight cyanosis, rusty sputum and he looked acutely ill. His throat was injected and over his right apex, down to the third rib, he showed dullness and diminished intensity of breath sounds. His expiratory sounds were bronchial in character, as was his whispered and spoken voice, and his fremitus was slightly increased. Numerous crepitant râles were heard on inspiration. A Roentgen ray plate showed engorgement of his entire right lung. Type II pneumococcus was recovered from his sputum.

The chart shows that on November 19 he had a marked relapse with rise of temperature to 103° F., an increase of immature polymorphonuclears to 49 per cent and a depression of lymphocytes (10 per cent), monocytes (5 per cent) and eosinophils (0 per cent). On the next day his monocytes began to rise and attained 17 per cent within 2 days, as his immature polymorphonuclears fell. As his convalescence progressed his lymphocytes and eosinophils began to increase in number. Unfortunately this patient left the hospital before his further course could be studied. But in patients who have been followed a lymphocyte count above 40 per cent persists often for weeks.

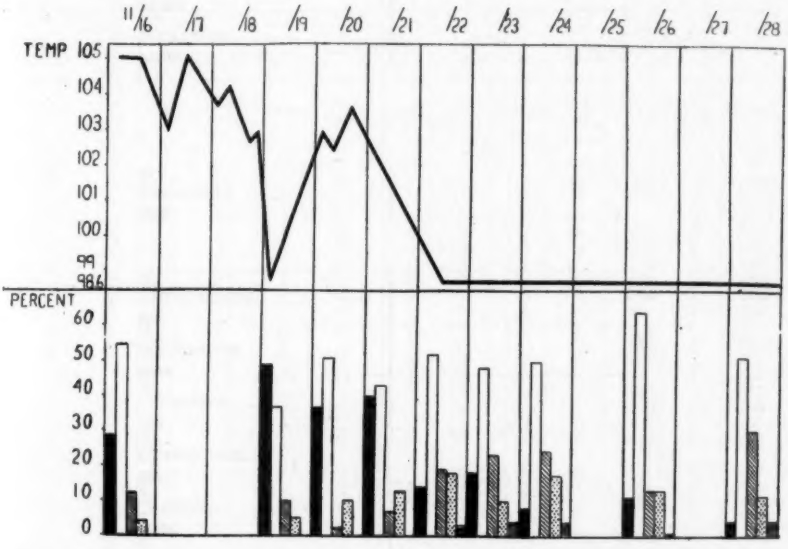

CHART III.—Hemogram of patient S. K., who recovered from lobar pneumonia.

TABLE 3.—HEMOGRAM OF CASE 2; RECOVERED FROM LOBAR PNEUMONIA.

Date.	W.B.C.	Immature polys.		Adult polys.		Lympho-cytes.		Monocytes.		Eosinophils.	
		Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.
1928											
Nov. 16 . .	26.0	29	7.5	55	14.3	12	3.1	4	1.0	0	0
19 . .	18.3	49	9.0	36	6.6	10	1.8	5	.9	0	0
20 . .	31.0	37	11.5	51	15.8	2	.6	10	3.1	0	0
21 . .	32.8	40	13.1	42	13.8	6	2.0	12	3.9	0	0
22 . .	18.8	13	2.4	51	9.6	19	3.6	17	3.2	2	.375
23 . .	17.4	18	3.1	47	8.2	22	3.8	10	1.7	3	.525
24 . .	14.1	7	1.0	50	7.1	23	3.2	16	2.3	4	.550
26 . .	13.0	11	1.4	64	9.3	12	1.6	12	1.6	1	.125
28 . .	9.1	4	.35	51	4.6	30	2.7	11	1.0	4	.350

The next 3 cases illustrate one of the most interesting features of the hemogram, its meaning in complications.

CASE 3.—The first of these, shown by Chart IV and its accompanying Table 4, represents the findings in a woman (V. S.), aged 39 years,

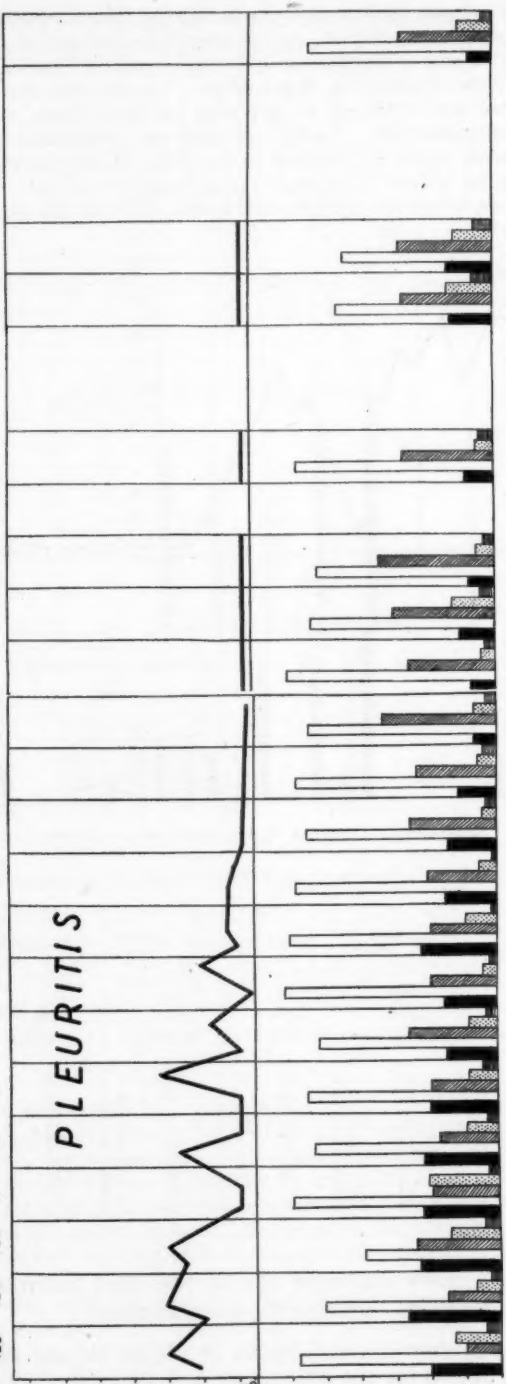

CHART IV.—Hemogram of patient V. S., who recovered from pneumonia after a complicating pleuritis.

admitted for pain in her right chest, chilliness, fever and general muscular pain for 4 days. Previous to this acute onset she had a productive cough for 2 months and complained of occasional head colds. On examination she appeared acutely ill, dyspneic and had rusty sputum. Her right side from the second to the eighth rib posteriorly was dull and the voice sounds were increased in intensity. Fine râles were scattered over this area. The blood culture was negative and the sputum showed Type II pneumococcus.

TABLE 4.—HEMOGRAM OF CASE 3; RECOVERED FROM PNEUMONIA AFTER A COMPLICATING PLEURITIS.

Date.	W.B.C.	Immature polys.		Adult polys.		Lympho-cytes.		Monocytes.		Eosinophils.	
		Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.
1930											
Nov. 28	12.7	20	2.5	57	7.2	10	1.3	12	1.5	2	.250
29	7.2	27	1.9	50	3.6	15	1.1	7	.5	1	.075
30	9.6	22	2.1	38	3.6	23	2.2	14	1.3	2	.200
Dec. 1	12.0	21	2.5	58	7.1	9	1.1	10	1.2	2	.250
2	16.0	21	3.4	52	8.3	16	2.6	8	1.3	2	.325
3	11.0	19	2.1	55	6.1	19	2.1	7	.775	2	.225
4	8.2	14	1.1	51	4.2	25	2.1	7	.575	2	.150
5	8.1	15	1.2	60	4.9	19	1.5	4	.325	1	.075
6	10.8	11	1.2	60	6.5	19	2.1	8	.85	1	.100
7	8.0	15	1.2	58	4.6	20	1.6	5	.4	1	.075
8	12.8	14	1.8	55	7.0	25	3.2	3	.375	2	.250
9	7.6	11	.85	58	4.4	22	1.7	5	.375	3	.225
10	7.8	6	.45	54	4.2	32	2.5	6	.45	2	.150
11	6.0	7	.425	60	3.6	25	1.5	4	.25	3	.175
12	5.5	10	.55	53	2.9	29	1.6	7	.4	3	.150
13	8.1	7	.575	51	4.1	33	2.7	5	.4	3	.250
18	6.7	8	.525	57	3.8	26	1.7	5	.325	4	.250
1931											
Jan. 21	5.8	12	.7	43	2.6	26	1.5	13	.75	6	.350
22	6.1	13	.8	43	2.6	27	1.6	11	.675	5	.300
Feb. 17	4.7	7	.325	53	2.5	27	1.2	10	.475	3	.150

The important features of this case are: (*a*) The maintenance of a fairly high immature polymorphonuclear count with the initial defervescence (December 1, 1930) suggesting a possible complication, followed by rather marked pleuritis; (*b*) the failure of a sustained high lymphocyte count; (*c*) the early appearance and persistence of eosinophils. This type of patient, who convalesces slowly, or develops a complication following the acute illness, invariably shows a tardy response of lymphocytes.

CASE 4.—P. C. represents another case in which there is a difficulty in maintaining a sustained lymphocytosis during convalescence. This patient had a left lower lobar pneumonia with Friedländer bacillus as a causative organism. Although at times he would show as many as 39 per cent lymphocytes, this was transitory and they would sink soon below 20 per cent. Not for 2 months did he show a high sustained lymphocyte count. This organism is prone to cause chronic pulmonary abscesses, and during this patient's convalescence he frequently expectorated large amounts of pus and Roentgen ray films showed suggestive shadows. It was not surprising, therefore, that 5 months after discharge he returned with an acute infection, chest pain and Friedländer bacilli were still recoverable from his sputum. Table 5 shows the blood counts.

TABLE 5.—HEMOGRAM OF CASE 4; FOLLOWING A PULMONARY FRIEDLÄNDER BACILLUS INFECTION, DEVELOPED A RELAPSE AFTER SEVERAL MONTHS.

Date.	W.B.C., total.	Immature polys.		Adult polys.		Lympho-cytes.		Monocytes.		Eosinophils.	
		Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.
1930											
Oct. 18 . .	20.6	20	2.5	26	5.6	20	4.1	30	12.6	4	.825
19 . .	13.8	14	1.9	32	4.4	25	2.1	27	3.7	2	.275
20 . .	23.2	21	4.9	31	5.4	29	7.0	17	3.9	2	.450
21 . .	22.0	24	5.3	44	9.9	20	4.4	10	2.2	2	.450
22 . .	18.0	13	2.3	41	7.4	32	5.8	10	1.8	3	.550
23 . .	22.8	8	1.8	58	13.2	22	5.0	10	2.3	2	.450
24 . .	24.6	8	2.0	64	16.2	22	5.4	4	1.0	2	.500
25 . .	13.8	8	1.1	63	8.8	20	2.8	8	1.1	1	.150
26 . .	15.6	9	1.4	52	8.3	29	3.5	8	1.2	2	.300
27 . .	11.2	6	.675	47	5.4	36	4.0	9	1.0	2	.225
28 . .	17.0	6	1.0	59	10.0	27	4.6	6	1.0	2	.350
29 . .	16.6	9	1.5	49	8.1	32	5.3	8	1.3	2	.325
30 . .	20.6	8	1.6	37	7.6	39	8.2	14	2.9	2	.400
31 . .	18.4	9	1.7	48	9.0	30	5.5	11	2.0	2	.350
Nov. 1 . .	10.8	7	.75	51	5.8	29	4.1	9	.975	4	.425
3 . .	13.0	8	1.0	51	6.8	30	3.9	8	1.0	3	.400
4 . .	16.0	5	.8	62	10.1	18	2.9	12	1.9	3	.475
1931											
Jan. 9 . .	9.8	5	.5	40	3.9	42	4.1	9	.875	4	.400
11 . .	8.7	7	.6	38	3.5	36	3.2	14	1.2	5	.450
Discharged											
May 18 . .	12.4	23	2.9	46	5.7	15	1.9	13	1.6	2	.250

CASE 5.—A man (F. R.), suffering from Type I pneumococcus, with 300 colonies per cubic centimeter of blood, recovered from his acute pulmonic condition after being given massive doses of serum and developed a post-pneumonic arthritis. Table 6 is an abbreviated account of his hemogram which was studied daily. On admission (January 20, 1931) he had a fairly low total count and had a marked "shift to the left" with a depression of lymphocytes, monocytes and eosinophils and his temperature was 104° F. For the next 5 days his condition continued precarious, with sustained fever, marked "shift to the left" and his total white blood count increased. On January 24 his culture was negative, his temperature dropped to 100° F. on January 25 and his immature polymorphonuclears decreased markedly on January 26. Although the patient felt very much better at that time, nevertheless there was no further reduction of immature polymorphonuclears and no rise in monocytes. On February 2 he complained of left sternoclavicular and shoulder-joint pain which was at first considered a serum reaction. However, this pain did not disappear and it was not until February 8 that a moderate rise in monocytes occurred. During the next few days many boils appeared, widely distributed over his body, which yielded Staphylococcus albus. On February 26 his lumbar joints were involved. Daily counts were performed until his discharge, and although he had an occasional lymphocyte rise (March 7 and March 15) this was only transitory and the same was true of the eosinophil response (March 16 and March 21). When he was finally discharged to a convalescent home (March 23), 2 months after admission, he still had an abnormally high immature polymorphonuclear count, a low lymphocyte count and functional and Roentgen ray evidence of a chronic inflammatory process of the left shoulder, sternoclavicular and of the lumbar vertebral joints.

The striking facts of this case are the persistence of a high immature polymorphonuclear count and the failure of the lymphocytes

to rise. The latter finding is almost diagnostic of delay in the convalescent phase.

TABLE 6.—HEMOGRAM OF CASE 5; SUFFERING FROM PNEUMONIA, DEVELOPED POLYARTHRITIS DURING RECOVERY.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lympho-cytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1931						
Jan. 20	7.4	37	55	6	2	0
21	18.2	72	22	5	1	0
22	15.8	76	21	2	1	0
23	21.0	59	35	5	1	0
24	16.2	46	48	4	2	0
25	13.8	53	35	6	3	1
26	12.6	30	47	13	7	0
28	13.4	26	67	3	4	0
30	9.8	25	56	11	6	1
Feb. 2	11.0	23	61	9	5	1
8	12.4	20	49	17	12	0
13	9.0	21	54	18	6	1
15	14.4	25	55	14	5	0
17	13.4	26	60	10	4	0
19	9.0	16	55	19	8	1
21	9.1	14	63	19	3	1
23	8.4	21	62	12	5	0
25	11.1	22	47	20	8	2
26	13.0	18	53	19	8	1
Mar. 6	9.6	19	58	10	10	1
7	13.0	13	40	31	13	2
8	11.3	14	56	17	10	2
14	13.3	21	49	18	9	3
15	11.6	15	43	27	11	3
16	15.2	24	51	14	6	4
17	13.6	21	51	15	10	2
21	11.3	22	48	19	6	5
22	11.0	25	53	12	7	2
23	11.2	20	51	18	10	1

While delay in convalescence is being considered it might be of interest to present the hemograms of 2 patients suffering from acute rheumatic fever. (Chart V and Table 7; and Table 8.) Both per cent and total values are charted in Chart V to show that no appreciable difference can be demonstrated graphically.

CASE 6.—J. O'C. was admitted suffering from joint pain of a few days' duration. He responded well to salicylates, his temperature dropped promptly and he left the hospital against advice 15 days after admission. One day after discharge his pain recurred and he entered the ward 1 week later with a distinct cardiac lesion. After a week in the hospital he left again against advice and returned 5 days later to the out-patient department with moderate pain, but refused to enter the ward.

The hemogram (Chart V, Table 7) shows that at no time did his immature polymorphonuclears fall to normal. His monocytes were high early in his illness, a characteristic of joint involvement. His lymphocytes

began to rise, suggesting beginning convalescence, but this increase was not sustained. He had an occasional eosinophil rise.

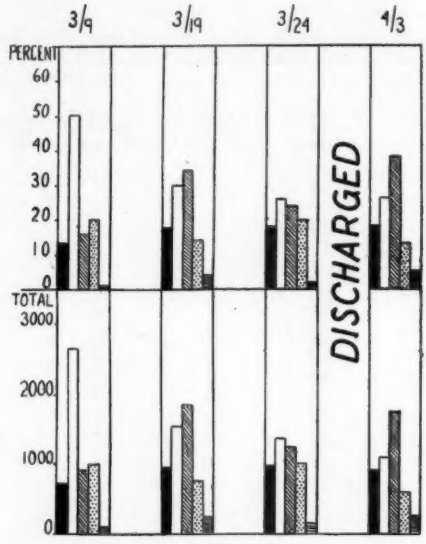

CHART V.—Hemogram of patient J. O'C., suffering from rheumatic fever, who developed a cardiac lesion.

TABLE 7.—HEMOGRAM OF CASE 6; SUFFERING FROM RHEUMATIC FEVER, DEVELOPED A CARDIAC LESION.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lympho-cytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1931						
Mar. 9 . .	5.3	13	50	16	20	1
19 . .	5.3	18	30	34	14	4
24 . .	5.0	18	26	24	20	2
Left the hospital against advice						
Apr. 3 . .	4.6	18	26	38	13	5
10 . .	6.9	17	24	43	14	2
Left the hospital against advice						
Apr. 5 . .	10.2	10	61	24	4	0
O. P. D. .						

CASE 7.—J. D. was admitted to the ward with acute joints and insisted upon leaving 1 week after admission because he felt perfectly well. But 5 days later he returned not only with acute joints but with signs suggestive of a mitral lesion. This time he remained in bed for 6 weeks. He returned 3 weeks after discharge to the out-patient department feeling well. This patient's hemogram (Table 8) indicated no evidence of convalescence upon his first discharge from the hospital. But on his return to the out-patient department his hemogram suggested that he was in a convalescent stage as judged principally by his high lymphocyte count. It is of interest to note that in this case there was very little rise in monocytes, a marked increase of which is common in joint involvement, but a

characteristic eosinophilia was present which is typical in most rheumatic fever patients. This patient's sedimentation rate, corrected for cell volume, was 1.9 on February 28, 1931 and 0.48 on March 15. The latter rate is found in convalescents.

TABLE 8.—HEMOGRAM OF CASE 7; HAD A RELAPSE IN THE COURSE OF RHEUMATIC FEVER.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1931						
Mar. 12 . .	6.2	13	47	29	7	3
14 . .	11.5	10	70	15	4	1
16 . .	8.0	12	54	22	7	5
19 . .	10.8	16	44	29	7	4
Left the hospital against advice						
Mar. 24 . .	5.8	14	30	37	10	8
Apr. 2 . .	8.4	11	41	34	7	7
9 . .	7.0	8	45	34	6	7
16 . .	5.2	10	47	30	6	6
23 . .	8.4	19	45	25	5	6
May 5 . .	9.5	5	43	37	8	5
Discharged						
May 22 . .	7.8	8	43	42	5	3
O. P. D.						

The problem of the relationship of lymphocyte rise to convalescence is of great importance in handling patients. This is especially true in those conditions in which serious complications may ensue if a patient is considered fully recovered too quickly. In this connection it is of interest to present the following case:

TABLE 9.—HEMOGRAM OF CASE 8; SUFFERED FROM RHEUMATIC FEVER AND LEFT THE HOSPITAL WHILE STILL CONVALESCING.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1930						
Nov. 18 . .	6.7	12	58	20	9	1
19 . .	10.2	5	62	25	7	1
20 . .	7.8	8	51	22	18	1
21 . .	8.7	4	56	26	12	2
22 . .	4.5	3	51	35	9	2
23 . .	9.5	4	50	31	12	3
24 . .	6.9	3	43	46	4	4
25 . .	6.9	3	58	35	3	1
26 . .	7.6	3	44	42	8	3
27 . .	7.1	2	46	45	5	2
28 . .	7.4	4	33	50	8	5
Dec. 1 . .	6.3	4	42	44	7	3
5 . .	7.7	2	44	44	6	4

CASE 8.—A young man (C. C.), who came in suffering from acute rheumatic fever, defervesced rapidly, showed no evidence of joint involvement

in a few days and his immature polymorphonuclear count became normal 2 days after admission and 6 days after the onset of his illness. However, his lymphocyte count (Table 9) which rose promptly was still high when he was discharged. Unfortunately he did not return for further study.

It might be of interest to study some other hemograms which show characteristic features. The findings in acute tonsillitis are striking.

CASE 9.—Table 10 illustrates the blood counts in an adult female (A. W.), admitted with a temperature of 102° F. and an acutely inflamed throat. Within 48 hours her temperature dropped and her general and local condition improved. In about a week she felt normal.

TABLE 10.—HEMOGRAM OF CASE 9; SUFFERED FROM ACUTE TONSILLITIS.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lympho-cytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1929						
Nov. 30	12.0	27	49	12	11	1
Dec. 1	8.2	27	38	15	15	5
2	5.9	27	25	29	12	7
3	5.2	11	32	38	13	6
4	7.1	13	48	24	8	7
5	6.2	5	48	33	10	4
9	8.9	4	39	41	12	4
12	6.4	6	40	39	14	1
16	5.2	4	36	46	9	5
18	6.4	5	49	36	6	4

CASE 10.—Table 11 shows a hemogram of a young male (J. S.), who developed acute tonsillitis during the course of convalescence from typhoid fever. He ran a fever varying from 101° to 104.5° F. for 4 days. His hemogram starts on the third day of his acute illness.

TABLE 11.—HEMOGRAM OF CASE 10; DEVELOPED ACUTE TONSILLITIS DURING THE COURSE OF CONVALESCENCE FROM TYPHOID FEVER.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lympho-cytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1930						
Oct. 14	14.6	23	50	21	5	1
15	12.4	13	39	29	13	6
16	9.5	8	32	47	9	4
17	10.0	9	41	34	7	9
18	13.6	10	31	34	8	17
19	13.0	9	39	40	6	6
20	13.7	9	47	28	6	10
23	15.4	6	45	37	7	5
25	13.8	4	43	38	5	10
27	10.6	5	43	40	4	8
29	7.1	6	36	48	4	6
Nov. 1	9.5	3	37	50	4	6
6	14.4	3	41	39	11	6
24	8.1	3	43	38	5	11

In both cases the striking feature is a high and sustained eosinophil count and the rapid attainment of a high lymphocyte count immediately upon recovery or almost as soon as the immature polymorphonuclears dropped to normal.

The next 2 cases illustrate the hemograms in 2 patients suffering from meningococcus meningitis.

CASE 11.—Table 12 shows the blood findings in a Puerto Rican girl (I. L.), aged 14 years, who was acutely ill on admission and responded rapidly to serum. The counts of November 21 and November 26 were performed during her reaction to serum.

TABLE 12.—HEMOGRAM OF CASE 11; SUFFERED FROM MENINGOCOCCUS MENINGITIS.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lympho-cytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1928						
Nov. 6 . .	11.7	36	44	9	10	1
9 . .	10.4	31	22	30	15	1
12 . .	15.4	23	47	23	5	2
13 . .	15.1	11	60	22	3	4
14 . .	19.4	6	59	25	9	1
16 . .	11.2	6	45	37	9	3
21 . .	7.3	10	44	39	5	2
26 . .	8.2	5	33	55	2	5

CASE 12.—Table 13 gives the findings in the case of a boy, aged 12 years (R. G.), during his convalescence.

In both patients a high lymphocytic count was obtained as convalescence progressed and an increase of eosinophils.

TABLE 13.—HEMOGRAM OF CASE 12; SUFFERED FROM MENINGOCOCCUS MENINGITIS.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lympho-cytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1930						
Nov. 11 . .	5.9	8	50	25	15	2
12 . .	3.3	7	55	27	6	5
13 . .	3.8	5	56	28	8	3
14 . .	4.6	6	51	33	6	4
15 . .	4.0	6	44	39	6	5
16 . .	6.1	7	41	40	9	3
20 . .	5.5	6	41	39	10	4

CASE 13.—Table 14 shows the results obtained in a male patient (T. N.), aged 66 years, who developed a lymphangitis of his right leg following a superficial injury. His temperature was 103° F. on admission and dropped, after local treatment, in 4 days. This hemogram shows the occurrence of a high eosinophil count early in recovery and the maintenance of a high lymphocyte count for a considerable period after his immature polymorphonuclears returned to normal.

TABLE 14.—HEMOGRAM OF CASE 13; DEVELOPED LYMPHANGITIS.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lympho-cytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1930						
Oct. 9 . .	6.9	33	34	12	19	2
10 . .	11.0	28	48	7	15	2
11 . .	10.0	15	57	12	11	5
12 . .	9.3	16	24	27	27	6
13 . .	8.2	17	34	23	19	7
14 . .	6.5	11	52	26	7	4
15 . .	9.3	9	36	44	8	3
16 . .	9.1	5	28	52	12	3
17 . .	8.9	3	43	36	14	4
18 . .	14.9	5	43	42	9	1
19 . .	8.0	5	26	57	9	3
20 . .	11.5	4	41	49	5	1
21 . .	9.1	7	39	48	5	1
22 . .	8.6	4	47	43	4	2
24 . .	10.6	7	42	48	2	1

TABLE 15.—HEMOGRAM OF CASE 14; SUFFERED FROM SCARLET FEVER.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lympho-cytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1929						
Nov. 22 . .	8.3	28	60	5	4	4
23 . .	8.2	30	50	8	8	4
24 . .	10.6	37	41	10	7	5
25 . .	15.7	32	47	6	10	5
26 . .	15.5	19	51	15	13	2
27 . .	15.0	17	52	13	16	2
28 . .	17.0	13	58	14	12	3
29 . .	14.0	17	49	16	16	2
30 . .	11.8	11	57	16	13	3
Dec. 1 . .	18.1	10	72	10	5	3
2 . .	12.8	10	61	10	15	4
3 . .	15.3	7	66	16	9	2
4 . .	12.0	6	67	16	7	4
5 . .	9.6	6	45	26	14	9
6 . .	11.5	5	61	18	11	5
7 . .	14.9	5	66	14	14	1
8 . .	13.0	3	63	17	12	5
9 . .	10.9	3	65	18	7	7
10 . .	8.5	1	52	29	10	8
11 . .	9.1	4	49	27	11	9

CASE 14.—Table 15 illustrates the findings in a female patient (G. P.), suffering from scarlet fever. The interesting features of this hemogram are the prolonged absence of an adequate lymphocyte response and the maintenance of a high eosinophil count. This patient entered the hospital with a temperature of 104° F. In 8 days it dropped to normal. Two days later she received news that her child died and she had a severe emotional reaction. Although her temperature rose to 103° F., her hemogram

showed no change. In the opinion of Professor Schilling her hemogram represented a typical illustration of recovery from the acute illness, but the failure of a marked lymphocytic rise to occur indicated a delay in convalescence.

The next 2 cases illustrate the effect of minor complications on the hemogram during the course of convalescence.

CASE 15.—Table 16 represents the blood counts in a patient (H. P.), suffering from acute lobar pneumonia during the course of his recovery. This was uneventful and he showed a typical recovery hemogram with a return of his immature polymorphonuclears to normal ("shift to the right") and rise of his lymphocytes. On February 18, 1931, he returned to the follow-up clinic complaining of an upper respiratory infection and a pain in his chest. The latter was found to be due to a slight pleuritis. It is of interest to note that his immature polymorphonuclears showed a distinct increase and that his lymphocytes and monocytes were markedly depressed.

TABLE 16.—HEMOGRAM OF CASE 15; DEVELOPED A PLEURITIS 3 MONTHS AFTER RECOVERY FROM AN ATTACK OF LOBAR PNEUMONIA.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lympho-cytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1930						
Nov. 18 . .	11.4	14	71	11	3	1
19 . .	8.1	12	71	8	8	1
20 . .	12.8	7	75	12	5	1
21 . .	16.9	9	56	26	8	1
22 . .	6.2	5	57	25	12	1
23 . .	8.8	4	66	17	11	2
24 . .	5.8	3	71	19	5	2
25 . .	8.7	10	70	13	5	2
26 . .	5.5	5	41	34	16	4
27 . .	6.5	4	48	40	5	3
28 . .	4.3	2	49	34	10	5
Dec. 9 . .	7.6	6	46	39	8	1
1931						
Feb. 18 . .	13.0	12	70	15	0	2

CASE 16.—Table 17 illustrates a similar condition. This patient was a young man (G. S.), suffering from Type I pneumonia from which he made a rapid and uneventful recovery except for an attack of serum sickness. He returned regularly for examination after his discharge. On February 18, 1931, his count showed a slight "shift to the left," although his lymphocytes remained high. Two days after this visit he developed a severe tonsillitis. This finding is in keeping with the fact that the blood count will change as long as 48 hours before the patient shows symptoms or signs of an acute infection. This rapid response of the blood cells is also seen in this case during his serum sickness. On December 14, 1930, a count was performed showing a sudden depression of his total count and a marked increase of his eosinophils. The blood was obtained for examination at 10 A.M. Not until 5 P.M., 7 hours later, did he develop urticaria and joint pain. When last seen this patient was in perfect condition and had a normal hemogram, including a normal lymphocyte count.

TABLE 17.—HEMOGRAM OF CASE 16; DEVELOPED AN ACUTE UPPER RESPIRATORY INFECTION AFTER CONVALESCENCE FROM LOBAR PNEUMONIA.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lympho-cytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1930						
Dec. 12 . .	6.0	24	49	14	10	3
13 . .	7.8	16	59	12	11	2
14 . .	4.7	11	63	12	9	5
15 . .	8.4	17	59	14	8	2
16 . .	6.0	9	45	27	17	2
17 . .	10.8	7	41	38	13	1
18 . .	4.7	8	41	40	10	1
21 . .	7.8	7	47	35	7	4
24 . .	7.6	5	57	28	8	2
25 . .	5.8	7	51	33	7	2
29 . .	6.0	6	52	32	6	4
1931						
Jan. 13 . .	8.4	5	50	35	6	4
28 . .	6.2	6	44	38	11	1
Feb. 18 . .	4.6	10	41	36	12	1
Mar. 25 . .	7.0	4	61	28	5	2

Discussion. In a recent Harvey address Gay[6] has emphasized the importance of the cellular reaction of the body to infection and pointed out that in the response of the blood and tissue cells we have our most delicate indication of the defense mechanisms. Schilling[7] has extended this view to convalescence. His hemogram gives us an excellent indication of the three phases in recovery from an infection—subsidence of the acute stage, convalescence, complete recovery.

This principle has been used extensively in the study of tuberculosis. This disease lends itself especially well for such research because patients have been educated to take a long convalescence from the tuberculous infection. Cunningham and Tompkins[8] and Durel[9] pointed out the importance of a low monocyte-lymphocyte ratio for favorable prognosis. Bredick[10] applied the details of the Schilling hemogram to tuberculosis, and concluded that this was the best single guide of the progress of the disease. Dunlop[11] came to the same conclusion. Brock[12] and Guggenheim[13] pointed out that the acute septic state of tuberculosis shows the same blood picture as any other acute infection and that only as localization and recovery occur does the hemogram give special details of the progress of the patient. It should be emphasized, however, that tuberculosis shows no different hemogram even in convalescence than any other infection. Only the duration of the various phases differs. An important practical use of the hemogram was made by Griesbach.[14] He applied this to pneumothorax therapy and found

that the air might be removed with complete recovery after the lymphocytes return to normal. Doan and Sabin[15] have studied the relation of cell response in tuberculosis by using the chemical derivatives from the organism and have thrown much light on the mechanisms involved.

Stuppy, Cannon and Falk[16] report an interesting experiment showing, they believe, that the cellular response is allergic in nature. In their work they found that experimental pneumonia produced in rabbits caused the appearance mostly of polymorphonuclear cells in the lungs. If the rabbits were immunized first with vaccine the histologic picture presented mostly histiocytes and some eosinophils. This illustrates strikingly the variation of cellular response to the same infection with variation in resistance.

The relation of the various types of cells to each other is of great interest and importance. It is obvious that one type of cell can have a depressing influence on other types.[17] This is seen in the relatively as well as absolutely low lymphocyte and monocyte counts when there is a predominance of immature polymorphonuclears. Eosinophils are usually considered as evidence of some allergic effect.[18] Certainly it is true that in most conditions in which a distinct allergic response is seen one finds the highest and most sustained eosinophil count, *e. g.*, scarlet fever,[19] acute tonsillitis and erysipelas. Incidentally these conditions are all caused by some form of hemolytic streptococcus. In some cases of rheumatic fever eosinophilia is prominent during convalescence.[20,21] The importance of eosinophilia depends upon the relation of complications to an allergic state.[22,23]

The most important practical consideration in studying the hemogram is to remember that it is only one nonspecific laboratory factor and to be of any help in a general clinical consideration it is necessary to make sequential counts at frequent intervals rather than isolated determinations. What a patient shows at a particular moment is only of importance in so far as it throws light on the direction a patient is going.

Conclusions. 1. In recovery from an acute infectious disease three more or less distinct phases may be demarcated by the hemogram: subsidence of the acute stage, convalescence, complete return to normal.

2. The subsidence of the acute stage is characterized by a decrease in immature polymorphonuclears and a marked, even if transitory, rise in monocytes.

3. Convalescence is characterized by a normal immature polymorphonuclear count, a marked rise in lymphocytes (often above 40 per cent) and a variable eosinophilia.

4. Complete recovery is characterized by a return of the lymphocytes to a normal range.

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ACHLORHYDRIA WITH A REVIEW OF 210 CASES IN PATIENTS WITH GASTROINTESTINAL COMPLAINTS.*

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Following the introduction of the fractional method of gastric analysis by Rehfuss,[1] it soon became obvious that a diagnosis of achylia gastrica based upon a single extraction of stomach contents was often erroneous. Eggleston[2] in a large series of cases compared the Rehfuss method with the older single extraction Ewald test and noted the incidence of achlorhydria to be twice as great by the latter method. Later it was found that a single fractional analysis is not infallible in the diagnosis of achlorhydria, since repeated examinations with the same or different test meals often gave a variable secretory response. The use of histamin as a gastric stimulant by Popielski[3] in 1920 and Carnot, Koskawski and Liebert[4] in 1922 made it possible to measure accurately the function of the stomach glands. In 1925 Gompertz and Voorhaus[5] applied the subcutaneous injection of histamin for the purpose of differentiating true from so-called false achylia. In a comparative study between the ordinary fractional analysis and a fractional analysis following the injection of histamin, two of us[6] have shown that only 53 per cent of stomachs in which achlorhydria was diagnosed after the Rehfuss test failed to secrete gastric juice after histamin injection. The increased accuracy thus available has shown that achylia gastrica is a comparatively rare condition and has made it possible to clarify the existing state of confusion in describing deficiency in gastric secretion.

This report comprises a review of 210 cases of achlorhydria occurring in patients with gastrointestinal complaints. The cases were selected promiscuously from our service in two large city hospitals and from private practice. The diagnosis of achlorhydria was based upon finding no free hydrochloric acid by fractional gastric analysis. In each instance the fasting gastric residuum was extracted and a meal consisting of 2 slices of ordinary white

* Read before the Pan-American Medical Association in Mexico City, July 29, 1931.

bread (35 grams) and 350 cc. of water was given. Extractions were removed every fifteen minutes for two hours unless the stomach emptied its contents into the duodenum previously. All patients upon whom gastric surgery had been performed were excluded.

Sex and Age Incidence of Achlorhydria in Health and Disease. Strangely enough, there is a paucity of literature on the probable expectancy of this condition. In much of the older literature the diagnosis was based upon a single extraction of the stomach contents. The aggregate of existing reports indicates a gradually increased incidence of achlorhydria with age. Wright recovered acid from all but 4 of 250 children between the ages of 6 and 15 years. Bennett and Ryle[8] found achlorhydria in 10 per cent of healthy students. Its frequency is variously given after the age of

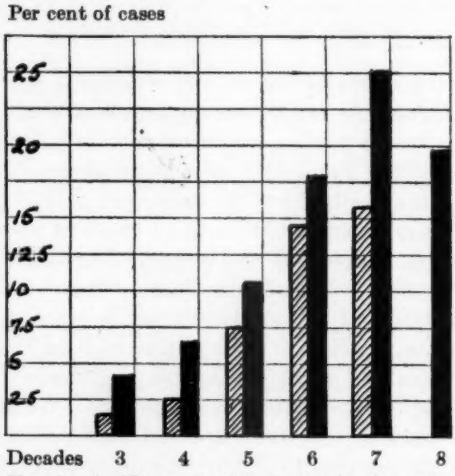

CHART I.—Showing incidence of achlorhydria in the various decades. Our series ■ Compared with Vanzant's ■

50 years as 20 to 50 per cent. Vanzant[9] recently reviewed 3381 gastric analyses performed on patients with normal digestive tracts and the absence of any other condition which is ordinarily considered to modify gastric acidity. The incidence of achlorhydria increased from 4 per cent at the age of 20 years to approximately 26 per cent at the age of 60 years. Women were more subject to achlorhydria than men regardless of age. A decrease in its incidence was found after the age of 70 years. Sixty-one cases in our series were selected from the office files of one of us by going over a series of 1075 consecutive gastric analyses in which all of the data were available. Table 1 and Chart I compare this series of 61 cases with that of Vanzant. The incidence of achlorhydria in our series (5.7 per cent) is much lower than in Vanzant's (12.1 per cent). Her analyses were terminated in 105 minutes whereas ours were continued 2 hours unless the stomach became empty before the 2-hour

extraction. We excluded about 10 cases because of the presence of free acid in the 2-hour extraction. The tendency to increase with age was present in both series. The occurrence of achlorhydria increased gradually with advancing years up to the age of 70 years. Our incidence in the male sex was 4.8 per cent and in the female 6.6 per cent, compared with Vanzant's incidence of 10.8 per cent in the male and 13.8 per cent in the female sex.

TABLE 1.—SEX AND AGE INCIDENCE OF ACHLORHYDRIA IN 61 CASES (1075 CONSECUTIVE GASTRIC ANALYSES).

Male.

Age decades.	This series.			Vanzant's series.		
	Cases achlorhydria.	Total cases.	Per cent achlorhydria.	Cases achlorhydria.	Total cases.	Per cent achlorhydria.
0 to 9	0	1	0	0	0	0
10 to 19	0	10	0	0	0	0
20 to 29	1	118	0.85	8	331	2.4
30 to 39	5	169	3.0	14	401	3.5
40 to 49	7	122	5.7	46	466	9.9
50 to 59	9	83	10.8	64	352	18.2
60 to 69	4	39	10.3	60	259	23.1
70 to 79	0	5	0	9	45	20.0
Total	26	547	4.8	201	1854	10.8

Female.

0 to 9	0	0	0	0	0	
10 to 19	0	10	0	0	0	
20 to 29	2	115	1.7	12	250	4.8
30 to 39	4	186	2.1	37	389	9.5
40 to 49	10	113	8.8	35	278	13.0
50 to 59	13	75	17.3	58	320	18.0
60 to 69	6	26	23.0	54	196	27.6
70 to 79	0	3	0	6	31	19.4
Total	35	528	6.6	202	1464	13.8

Total Cases.

0 to 9	0	1	0	0	0	0
10 to 19	0	20	0	0	0	0
20 to 29	3	233	1.3	20	581	3.4
30 to 39	9	355	2.5	51	790	6.5
40 to 49	17	235	7.2	81	744	10.9
50 to 59	22	158	14.0	122	672	18.1
60 to 69	10	65	15.4	114	455	25.0
70 to 79	0	8	0	15	76	19.7
Total	61	1075	5.7	403	3318	12.1

Paradoxical as it may appear, one might conclude from this comparison that patients consulting a physician because of gastrointestinal complaints show a lower incidence of achlorhydria than a similar group of normal patients of like age and sex. One explanation may be that diseases giving rise to hyperacidity are a more common cause of gastrointestinal complaints than those producing anacidity. So-called hyperacidity is more often associated with disturbances of motility, a factor of greater importance in the production of symptoms than secretory deficiencies.

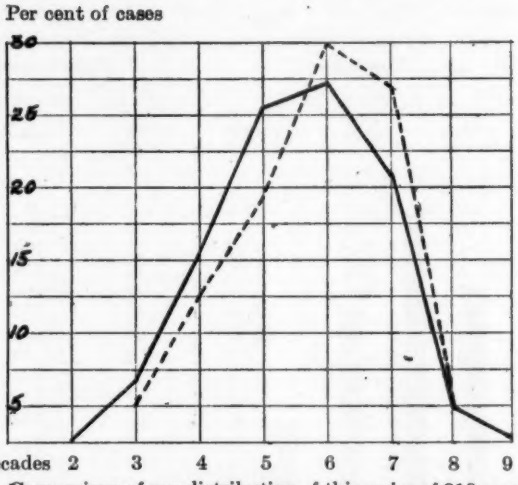

CHART II.—Comparison of age distribution of this series of 210 cases of achlorhydria with Vanzant's series of 403 cases in normals.
This series ——— Vanzant's - - - - -

TABLE 2.—AGE COMPARISON OF 210 CASES OF ACHLORHYDRIA IN OUR PATIENTS WITH 403 CASES OF ACHLORHYDRIA IN NORMAL INDIVIDUALS (VANZANT'S).

	Achlorhydria in our patients.		Achlorhydria normal people (Vanzant).	
Decade.	Number.	Per cent.	Number.	Per cent.
0 to 9	0	0	0	0
10 to 19	1	0.5	0	0
20 to 29	15	7.1	20	5.0
30 to 39	32	15.2	51	12.7
40 to 49	53	25.2	81	20.1
50 to 59	57	27.2	122	30.0
60 to 69	43	20.5	114	28.4
70 to 79	7	3.3	15	3.8
80 to 89	2	1.0	0	
Total	210		403	

Age Incidence of Cases With Achlorhydria. In our entire series of 210 cases of achlorhydria, 100 cases occurred in the male sex and 110 in the female sex. The age decades in which these cases occurred can be compared with a series of 403 cases reported by Vanzant (Table 2). The highest decade incidence in each series was the

sixth. Seventy-three per cent of our series and 78.5 per cent of Vanzant's occurred between 40 and 70 years. However, 48 per cent of our cases and only 37.5 per cent of Vanzant's were under 50 years of age. (See Chart II.)

The available literature based upon a study of the whole period of gastric digestion, shows a very low incidence of achlorhydria in childhood and a gradually increasing frequency up to the age of 60 years. One infers that the condition usually develops during later life and is rarely congenital and this is supported by the work of Conner.[10] He found a greater frequency of achlorhydria among blood relatives of patients with pernicious anemia than among other people. His feeling that the achlorhydria was not in itself inherited was based upon finding only 15.7 per cent of achlorhydria in blood relatives under 40 years of age and 42.3 per cent in blood relatives after the age of 40 years. He concluded that the members of pernicious anemia families may inherit a tendency toward the development of achlorhydria later in life. If it were true that achylia gastrica is more apt to be congenital or hereditary, as some believe, one would expect to find a greater number of cases of true achylia in the earlier decades. We noted no essential difference between the age incidence of our cases of true achylia and of achlorhydria or pseudo-achylia.

Ordinary Fractional Gastric Analysis Compared with Histamin Gastric Analysis. The histamin test as described by two of us[6] was used in 64 cases in which the ordinary fractional gastric analysis had previously been carried out. From 0.25 to 1 mg. of histamin was injected simultaneously with the ingestion of the test meal. A physiologic response consisting of a diffuse erythema was considered essential. This is mentioned because Gaither[11] has recently reported finding an achlorhydria after histamin in several cases in which an acid response was obtained by test meals without histamin. We have never failed to get an acid response to histamin in every case in which acid was present by ordinary gastric analysis. It is our feeling that experience of the type reported by Gaither may result from the use of a preparation of histamin which has lost its potency or from the use of an insufficient dose. Such errors may be prevented by discarding all tests in which histamin does not provoke a general erythema. We used primarily from 0.25 to 0.5 mg. of histamin. If no reaction was observed, a second injection was given so that the total dose amounted to 1 mg. of histamin. A failure to obtain free acid and enzymes after histamin injection warrants a definite diagnosis of achylia gastrica and such a diagnosis is never justifiable without histamin.

An apparent achylia was indicated by the absence of both free acid and gastric rennet after ordinary gastric analysis in 58 of 64 cases in which histamin was subsequently used (Table 3). Of these (15 were cases of pernicious anemia) 35 failed to respond to

TABLE 3.—ORDINARY FRACTIONAL GASTRIC ANALYSIS COMPARED WITH FRACTIONAL ANALYSIS AFTER HISTAMIN.

Case No.	Age.	Sex.	Diagnosis.	Ordinary gastric analysis.			Secretory diagnosis based upon ordinary gastric analysis.	Histamin gastric analysis.			Secretory diagnosis after histamin.
				HCl.	Total acid.	Rennet.		HCl.	Total acid.	Rennet.	
1	60	M.	Intestinal stasis	0	15	0	Apparent achylia	0	20	0	Achylia
4	36	F.	Intestinal stasis	0	10	0	"	0	10	0	"
1	36	F.	Intestinal stasis	0	10	0	"	0	10	0	"
7	44	M.	Spastic colitis	0	15	0	"	0	15	0	"
16	51	F.	Gastrogenous diarrhea	0	15	0	"	0	15	0	"
17	27	M.	Cardiospasm	0	15	0	"	0	20	0	"
18	56	M.	Secondary anemia	0	10	0	"	0	10	0	"
22	39	F.	Pernicious anemia	0	20	0	"	0	30	0	"
28	59	F.	Diabetes	0	10	0	"	0	10	0	"
29	67	M.	Posterolateral sclerosis	0	10	0	"	0	10	0	"
35	62	M.	Pernicious anemia	0	20	0	"	0	15	0	"
45	50	F.	Secondary anemia	0	15	0	"	0	15	0	"
46	45	M.	Pernicious anemia	0	10	0	"	0	10	0	"
54	40	F.	Spastic colitis	0	20	0	"	0	15	0	"
62	42	M.	Pernicious anemia	0	15	0	"	0	10	0	"
64	45	M.	Gastrogenous diarrhea	0	10	0	"	0	10	0	"
70	68	M.	Alcoholic gastritis	0	15	0	"	0	10	0	"
71	41	F.	Intestinal stasis	0	10	0	"	0	20	0	"
75	50	F.	Hypertension	0	25	0	"	0	20	0	"
76	46	F.	Pernicious anemia	0	30	0	"	0	15	0	"
77	55	F.	Intestinal stasis	0	10	0	"	0	10	0	"
78	59	M.	Cardiac decompensation	0	25	0	"	0	10	0	"
86	44	M.	Intestinal stasis	0	10	0	"	0	10	0	"
90	28	M.	Psychoneurosis	0	10	0	"	0	10	0	"
91	64	F.	Pernicious anemia	0	10	0	"	0	10	0	"
92	65	F.	Gastrogenous diarrhea	0	10	0	"	0	10	0	"
102	62	F.	Cholecystitis	0	15	0	"	0	10	0	"
L 4	59	M.	Gastric lues	0	15	0		0	15	0	"
L 11	31	F.	Gastric lues	0	20	0	"	0	15	0	"
L 13	60	M.	Lues	0	20	0	"	0	25	0	"
L 15	51	F.	Lues	0	10	0	"	0	20	0	"
W 88	52	M.	Pernicious anemia	0	20	0	"	0	20	0	"
W 89	52	F.	Pernicious anemia	0	20	0	"	0	15	0	"
W 97	21	F.	Arthritis	0	25	0	"	0	15	0	"
W 100	45	F.	Duodenal ileus	0	10	0	"	0	15	0	"
W 102	46	F.	Pernicious anemia	0	30	0	"	0	10	0	"
61	52	M.	Secondary anemia	0	15	0	"	0	30	+	Achlorhydria
20	60	F.	Biliary cirrhosis	0	15	0	"	20	60	+	Hypochlorhydria
21	65	F.	Gastrogenous diarrhea	0	20	0	"	0	30	+	Achlorhydria
31	64	M.	Portal cirrhosis	0	15	0	"	0	25	+	"
39	34	F.	Hyperthyroidism	0	15	0	"	0	30	+	"
44	60	M.	Hypertension	0	20	0	"	0	20	+	"
47	25	F.	Gastritis	0	20	0	"	0	20	+	"
68	43	F.	Melena	0	10	0	"	0	10	+	"
80	39	M.	Gastritis	0	40	0	"	40	55	+	Normal acid
87	35	M.	Spastic colitis	0	20	0	"	5	25	+	Hypochlorhydria
89	55	M.	Arteriosclerosis	0	10	0	"	0	10	+	Achlorhydria
94	56	M.	Spastic colitis	0	20	0	"	0	20	+	"
97	76	M.	Gastritis	0	20	0	"	0	30	+	"
99	39	M.	Spastic colitis	0	15	0	"	0	10	+	"
101	33	F.	Splanchnoptosis	0	10	0	"	0	30	+	"
L 1	48	F.	Gastric lues	0	10	0	"	20	40	+	Hypochlorhydria
L 14	81	F.	Lues	0	15	0	"	0	20	+	Achlorhydria
L 16	42	M.	Lues gastric ulcer	0	25	0	"	0	25	+	"
W 83	48	M.	Secondary anemia	0	20	0	"	5	15	+	Hypochlorhydria
W 94	39	M.	Intestinal stasis	0	15	0	"	0	20	+	Achlorhydria
W 103	55	F.	Splanchnoptosis	0	15	0	"	0	15	+	"
9	33	M.	Intestinal stasis	0	15	0	"	0	25	+	"
L 8	42	F.	Gastric lues	0	10	0	"	35	60	+	Normal acid
L 3	21	M.	Gastric lues	0	20	+	Apparent achlorhydria	55	70	+	Hyperacidity
33	40	F.	Spastic colitis	0	20	+	"	0	25	+	Achlorhydria
42	60	M.	Gastric hemorrhage	0	40	+	"	10	50	+	Hypochlorhydria
49	43	F.	Auricular fibrillation	0	25	+	"	5	25	+	"
L 2	27	F.	Lues	0	15	+	Apparent achlorhydria	15	40	+	"
8	34	F.	Spastic colitis	0	20	+	"	0	15	+	Achlorhydria

The acidity figures recorded represent the highest values obtained throughout the two hour test.

histamin either by acid or enzyme secretion, giving true achylia in 60 per cent of cases in which an apparent achylia was found after ordinary fractional gastric analysis. Twenty-three cases (40 per cent) showed a secretory response to histamin. Gastric rennet without hydrochloric acid appeared in 17 cases (true achlorhydria). In 4 cases an hypochlorhydria and in 2 a normal acidity resulted from histamin injection. In 6 cases an apparent achlorhydria (enzymes present) was present without histamin. Histamin failed to cause acid response in 2, but in 3 cases a hypochlorhydria, and in 1 a hyperacidity followed the injection. Experience with histamin suggests a gradual rather than sudden development of achylia. The secretion of gastric enzymes apparently persists in many stomachs after acid secretion has stopped. Hydrochloric acid is never secreted in the absence of gastric enzymes. Histamin is capable frequently of producing acid response in many instances in which only enzymes are secreted after the ordinary meal or of causing only an enzyme secretion when both acid and enzymes are absent after the ordinary test meal. The state of gastric secretion as determined by histamin injection is rarely ever improved by treatment.

Although we cannot demonstrate that gastritis is the usual cause of true achylia, the evidence at hand suggests some cause acting over a long period of time. We have never observed the sudden appearance of achylia in a patient with normal gastric secretion a short time previously; but we have followed patients with a normal acidity through the stages of hypochlorhydria until an achlorhydria developed.

TABLE 4.—COMPARISON BETWEEN TWO ORDINARY FRACTIONAL GASTRIC ANALYSES (19 CASES).

Case No.	Age.	Sex.	Diagnosis.	First analysis.			Secretory diagnosis first analysis.	Second analysis.			Secretory diagnosis second analysis.
				HCl.	Total acid.	Rennet.		HCl.	Total acid.	Rennet.	
52	51	F.	Spastic colitis	0	20	0	Apparent achylia	0	25	+	Apparent achlorhydria
L 6	55	M.	Gastric lues	0	10	0	"	20	30	+	Hypochlorhydria
W 16	49	F.	Cholecystitis	0	5	0	"	0	5	0	Apparent achylia
W 69	25	F.	Pulmonary tuberculosis	0	20	0	"	15	25	+	Hypochlorhydria
3	60	F.	Cholecystitis	0	25	+	Apparent achlorhydria	0	25	+	Apparent achlorhydria
11	31	F.	"	0	15	+	"	0	20	+	"
50	43	M.	Intestinal stasis	0	15	+	"	0	20	+	"
53	48	M.	Spastic colitis	0	25	+	"	0	25	+	"
63	41	M.	Cholelithiasis	0	30	+	"	0	25	+	"
66	27	F.	Cholecystitis	0	5	+	"	0	30	+	"
69	74	M.	Benign hourglass	0	20	+	"	45	55	+	Normal acid
L 10	46	F.	Gastric lues	0	20	+	"	0	25	+	Apparent achlorhydria
99	58	M.	Carcinoma	0	25	+	"	15	40	+	Hypochlorhydria
W 2	30	F.	Splanchnoptosis	0	20	+	"	0	20	+	Apparent achlorhydria
W 18	51	M.	Intestinal stasis	0	15	+	"	0	20	+	"
W 23	37	F.	Intestinal stasis	0	15	+	"	15	30	+	Hypochlorhydria
W 50	56	F.	Cholecystitis	0	10	+	"	0	5	+	Apparent achlorhydria
W 52	47	F.	Cholelithiasis	0	20	+	"	0	15	+	"
W 79	62	M.	Carcinoma	0	15	+	"	45	70	+	Normal acid

The figures for acid values are the highest found during the analysis.

Recent publications by Gilman and Cowgill[12] and Vineberg and Babkin[13] indicate that in dogs with Pavlow or Heidenhain type pouches histamin acts exclusively on the acid secreting glands, and that following an initial rise in pepsin content, probably due to flushing of the glands, there is a decrease in pepsin concentration. Our experience in these cases, using the rather crude rennet test for gastric enzymes, suggests that in many cases of achlorhydria histamin does stimulate the enzyme secreting cells.

In 19 cases the ordinary fractional gastric analysis was repeated at least once without the use of histamin. The results of this study are tabulated in Table 4. In 7 of the 19 cases (37 per cent) the degree of secretory function was later found to be greater without resorting to histamin. This clearly emphasizes the fallacy of basing a diagnosis of achylia upon one fractional gastric analysis without using histamin.

TABLE 5.—INCIDENCE OF VARIOUS DISEASES AND SYMPTOMS OCCURRING IN 210 CASES OF ACHLORHYDRIA.

	Male		Female		
Diagnosis.	Achylia.	Achlor-hydria.	Achylia.	Achlor-hydria.	Total.
1. Pernicious anemia	6	0	9	0	15
2. Anemia (not primary)	3	8	4	14	27
3. Combined lateral sclerosis	2	2	1	0	5
4. Gastritis	2	26	3	10	41
4b. Duodenitis	3	27	4	19	53
5. Gastric lues	1	3	2	3	9
6. Tertiary lues	1	10	0	2	13
7. Cancer, stomach	0	9	0	7	16
8. Cancer, elsewhere	0	1	0	2	3
9. Cholecystitis	0	3	1	12	16
10. Cholelithiasis	0	3	0	4	7
10. Visceroptosis	0	2	3	18	23
11. Spastic colitis	3	11	1	7	22
12. Mucous colitis	1	3	0	3	7
13. Ulcerative colitis	0	2	0	0	2
14. Arteriosclerosis	1	7	1	1	10
15. Hypertension	0	6	1	3	10
16. Nephritis	0	3	0	1	4
17. Cardiac disease	1	3	1	6	11
18. Arthritis	0	3	2	3	8
19. Acne rosacea	0	1	0	0	1
20. Other dermatoses	0	0	0	3	3
21. Portal cirrhosis	0	3	0	0	3
22. Banti disease	0	0	0	1	1
23. Diabetes	0	0	1	4	5
24. Pulmonary tuberculosis	0	3	0	1	4
25. Constipation (not listed under spastic colitis)	7	23	3	31	64
26. Gastrogenous diarrhea	1	8	1	11	21
27. Duodenal stasis	0	1	2	4	7
28. Cardiospasm	1	0	0	3	4
29. Giardiasis	0	0	0	1	1
30. Goiter	0	0	0	2	2
31. Psychoneurosis	1	3	0	1	5
32. Gastric ulcer	0	1	0	0	1

Significance and Incidence of Various Diseases and Symptoms in 210 Patients with Achlorhydria. A complete list of the more important diagnoses made and of the conditions which are commonly thought to be associated with achlorhydria and achylia will be seen on Table 5.

Primary Pernicious Anemia. As early as 1886 Cahn and von Mehring[14] reported the absence of hydrochloric acid in a case of pernicious anemia. A true achylia gastrica (after histamin) is now generally considered to be a necessary accompaniment of this disease, although a few reports appear in the literature in which free acid or enzymes were recovered from the stomach. (Levine and Ladd[15] and Grinker[16]). The accuracy of the diagnosis in these cases is doubtful. Many observers (Faber,[17] Hurst[18] and Sturtevant[19]) have noted the existence of achlorhydria years previous to the onset of pernicious anemia. The cure of the anemia on liver therapy is not associated with a return of gastric acidity, according to most writers. Hurst, however, mentioned 3 cases in which acid reappeared after treatment. McPeak and Neighbors[20] had a case of pernicious anemia in which achylia was known to have been present for 4 years, yet acid was found in the stomach 4 months after liver therapy was started. Cases of this sort are undoubtedly very rare. Johansen,[21] Minot and Murphy,[22] Heath[23] and Ordway *et al.*[24] failed to note a disappearance of achylia after liver therapy.

There were 15 cases of pernicious anemia in the series. All had a true achylia gastrica, even on reëxamination after the institution of specific therapy. We have never observed a case of Addisonian anemia in which a true achylia gastrica was not present. In borderline cases we feel that the presence of acid or enzymes in the stomach rules out a diagnosis of primary anemia.

Case Reports. CASE 1.—One of the patients included in this report entered the Hospital with the typical picture of a primary anemia. The erythrocytes were 1,100,000 and the hemoglobin too low to estimate. He had the typical pallor and an atrophic glossitis. The spleen was palpable and signs and symptoms of a combined lateral sclerosis were present. The first gastric analysis showed no free acid or rennet. A provisional diagnosis of Addisonian anemia was made. However, the blood studies revealed a low color and volume index and a microcytosis. The gastric analysis was repeated with histamin and gastric rennet was recovered. The patient is improving steadily on nonspecific therapy without liver.

We found no evidence of gastritis in any case of pernicious anemia. Invariably the stomach was "clean." Naturally one cannot assume that the achylia did not originate as a gastritis. However, the familial incidence of pernicious anemia and the inability to find any evidence of gastritis suggest the occurrence of the achylia as an inherited trait which may not develop until later life.

Combined Lateral Sclerosis. Vanderhoof[25] feels that achylia gastrica is as constant a finding in acroparesthesia as it is in per-

nicious anemia. There are not enough case reports based upon conclusive evidence of the existence of achylia to warrant the acceptance of this view at present. There were but 5 cases of definitely established posterior lateral sclerosis in this series. Only 2 had a true achylia, 1 of which had pernicious anemia. Our finding of gastric rennet in 3 cases following histamin would indicate that true achylia is not necessary to the diagnosis.

Incidence of Anemia (Not Primary) in Achlorhydria and Achylia Without Obvious Cause. Davies and James[26] recorded the incidence of anemia in 32 normal people with achlorhydria, over 60 years of age. In a group of 14 cases without acid response to histamin, 7 had erythrocyte counts under 4,000,000 and hemoglobin less than 60 per cent. The lower the pepsin concentration the greater was the tendency toward anemia. In a second group of 13 cases with acid response to histamin only 3 cases showed a similar degree of anemia. Blood counts were performed on 119 of our cases in which there was no obvious cause for anemia. The erythrocytes were under 4,000,000 and the hemoglobin less than 60 per cent in 7 of 22 cases of true achylia and in 20 of 97 cases of achlorhydria. It is noteworthy that the tendency toward anemia in true achylia was much greater than in achlorhydria.

Gastritis. The gastric residuum was routinely examined for evidence of gastritis. If gastritis was suspected an astringent lavage of zinc chlorid and formalin was given. A record was made of the amount of gross mucus and the sediment examined microscopically for mucus, pus, bacteria and tissue fragments. If these elements were present in excess and could be identified as having originated in the stomach a diagnosis of gastritis was made. Of our cases 41 (28 male and 13 female) were so classified (19.5 per cent). Six cases were diagnosed gastric lues. In 5 of these a gastric defect was present by Roentgen ray; a provisional diagnosis of luetic gastritis was made in the sixth. In this case, 5 gastric analyses were performed over a period of 2 years, during which time luetic therapy was administered. Each analysis showed an achlorhydria (rennet present) after histamin. An ordinary gastric analysis after 3 years of therapy showed a return of free acid up to 35. Such a return of free acid which has been consistently absent after histamin injection over a period of 3 years is unique in our experience. Tertiary lues without gastric defect was present in 3 other cases. We feel with Wile[27] that a catarrhal gastritis in luetic patients with achlorhydria may represent the first stage of gastric syphilis. Response to antiluetic therapy in some cases confirms this view. Alcohol was a probable etiologic factor in 13 cases (32 per cent). Foci of infection in the mouth, nose and throat are thought by Hurst[28] and others to be an important causative factor in gastritis. Definite evidence of such infection was present in 24 cases (59 per cent). The site of infection was as follows: teeth 13 cases; tonsils

11 cases; advanced pyorrhea 9 cases; sinuses 3 cases and the nasopharynx 1 case. Multiple foci were not uncommon.

There was definite disease of the heart, kidneys or bloodvessels in 10 cases (24 per cent). Degenerative disease of the cardiovascular-renal apparatus is not infrequently associated with gastritis, offering one explanation for the gradually increasing incidence of achlorhydria up to the seventh decade. The reason for the decreasing incidence of achlorhydria after this age may very well be the exodus of such patients before the eighth decade.

Only 12 per cent of our cases with gastritis had a true achylia. Hurst[29] recovered free acid in 50 per cent of his cases of achlorhydria merely by repeating the examination after gastric lavage. He feels that this is accomplished by ridding the mucosa of adherent mucus which retards gastric secretion. We have confirmed his findings in a few cases. However, we do not feel with him that failure to recover acid or enzymes after this procedure is proof positive of constitutional achylia or primary atrophic gastritis. In 12 cases with gastritis an apparent achylia was found by ordinary gastric analysis. Histamin injection established a diagnosis of true achylia in 5 of them. Five were converted into achlorhydria, 1 into hypochlorhydria and 1 became a normal acidity after injection of histamin. Most cases of apparent achylia showing evidence of gastritis by examination of the residuum after ordinary gastric analysis will be found capable of gastric secretory response after appropriate stimulation or treatment. The incidence of anemia in the gastritis group was less than in that found in cases of achylorhydria without gastritis.

Duodenitis. Hurst mentions the frequency of duodenitis in cases of achlorhydria. Knott[30] feels that increased alkalinity of the intestinal contents in achlorhydria allows bacteria which are confined normally to the colon to ascend to the small intestine or even to the stomach. A considerable experience with cultures of bile obtained through a duodenal tube suggests to us another possible explanation for the finding of colon organisms in the duodenum in achlorhydria. It seems likely that normally many organisms are withdrawn from the portal stream by the liver and excreted in the bile without actually infecting the biliary tract. Normally they are destroyed in the duodenum by acid influx, but when the duodenal content is constantly alkalin, an implantation of organisms may readily occur. From duodenal cultures of 10 cases, a colon bacillus was recovered in 5 instances and a Streptococcus hemolyticus in association with a B. coli in another. By examination of the duodenal aspirate 82 per cent of cases of gastritis and 58 per cent of cases of the entire series showed evidence of a catarrhal duodenitis. This suggests that the gastritis itself is a factor of importance in the development of duodenitis in cases of achlorhydria.

Syphilis. Of 210 cases of achlorhydria 22 had tertiary lues (10.5 per cent). There were 9 cases in which gastric lues was suspected; in 2 others cerebrospinal involvement was present; 4 cases had a true achylia. Antiluetic treatment brought about an apparent improvement in gastric secretory function in 6 cases of achlorhydria by the appearance of acid after treatment. Achlorhydria is generally present in luetic gastritis and the "diffuse fibrosis" type of gastric lues. However, in cases of gastric ulcer[31] and pyloric stenosis which fulfill the established criteria for gastric syphilis, achlorhydria may not be present. When present in association with a lesion resembling ulcer the possibility of lues must always be considered.

Gastric Carcinoma. Hurst[32] believes that the achlorhydria which occurs in over one-half the cases of gastric cancer is not the result of the growth but due to an antecedent chronic gastritis. He considers gastritis the most common predisposing cause of cancer. He has never observed the development of achlorhydria in a case of gastric cancer in which hydrochloric acid was present at the onset. One patient in this series with a pyloric carcinoma had a fasting hyperacidity (hydrochloric 90, total acidity 115); 3 months later an achlorhydria was present with a total acidity of 65. The diagnosis was confirmed at operation. Both Hurst and Porges[33] report that development of carcinoma in patients known to have had achlorhydria previously. Hurst attempts to classify cases of gastric cancer into 2 groups: those with persistent gastric acidity and those with achlorhydria. The latter type is termed by him "gastritis-cancer," namely, cases with achlorhydria due to chronic gastritis and usually having a short history. He supports this contention by quoting Hartman,[34] who found 44 per cent of 39 cases of cancer with achlorhydria alive 5 years after gastrectomy and only 22 per cent of 41 cases with acid alive 5 years after resection. Hurst argues that if achlorhydria resulted from the cancer the cases without acid should have a poorer prognosis. He further mentions Orator's[35] finding of a diffuse atrophic gastritis involving the fundus as well as the pyloric region in 19 of 20 such cases. Hurst stresses the importance of a universal atrophic gastritis in the etiology of so-called "primary" cancer, which he feels should be called "gastritis-cancer."

We found 16 cases of gastric carcinoma in this survey of 210 cases of achlorhydria. Only 4 of them had an apparent achylia after ordinary fractional analysis; histamin was not used. The remainder were cases of apparent achlorhydria. In 10 of these the total acidity reached a high level of 25 or more. The achlorhydria of gastric carcinoma is characteristically associated with a high total acidity due to the presence of organic acid. The theory of Hurst is deserving of serious consideration to account for the large number of cases of cancer with achlorhydria. We are frequently

at a loss to explain the presence of achlorhydria in a patient with a small carcinoma in the region of the pylorus. However, the explanation is not any more obscure than an attempt to account for the achlorhydria which sometimes develops after resecting only a small portion of the distal end of the stomach. Crohn[36] believes that some disturbance of the innervation of the stomach probably accounts for the latter condition. It is obvious from a survey of our cases that an achlorhydria may be associated with any type of cancer anywhere in the stomach. That the achlorhydria may have antedated the malignancy in many cases cannot be denied.

It should be borne in mind that many cases of gastric carcinoma have considerable free acid and some an actual hyperacidity. Two of us[37] recently reported 3 cases in which ulcer and cancer of the stomach occurred independently, the cancer in each case involving the pylorus and the ulcer being higher up on the lesser curvature with normal mucosa intervening. All 3 had a very high gastric acidity.

Gall Bladder Disease. Cholelithiasis was formerly considered by many to be one of the more common lesions associated with achlorhydria. This has not been our experience. A fractional gastric analysis was performed on 62 cases of cholelithiasis proved by operation.[38] Hyperacidity was encountered in 32, normal acidity in 14, hypoacidity in 13, and achlorhydria in only 1 case. Only 7 cases of cholelithiasis (3 per cent) were found in this series of 210 cases of achlorhydria. True achylia was not encountered. A clinical diagnosis of cholecystitis was made in 16 cases. Most of them were not operated upon and the diagnosis was not confirmed. The incidence of achlorhydria was no greater in these cases of gall-bladder disease than it is in any like group of individuals of the same age and sex.

Visceroptosis. A clinical diagnosis of visceroptosis was made in 21 females and 2 males (11 per cent). The constitutional habitus was recorded in 164 cases; 78 (48 per cent) were asthenic; 61 (37 per cent) were sthenic and only 25 cases (15 per cent) were hypersthenic. The inference may be drawn that achlorhydria is more frequent in the *habitus asthenicus* and is very infrequent in people of the hypersthenic build. The presence of achlorhydria in a patient of hypersthenic habitus would appear to be of more clinical significance.

Colitis. Twenty-two patients had signs and symptoms of excessive spasticity of the colon, and so-called spastic or irritable colon. Seven had mucous colitis and 2 ulcerative colitis. Functional or organic disease of the colon was noted in 30 cases (14 per cent). In a series of 45 cases of mucous colitis recently analyzed[39] hypochlorhydria was present in 11 and achlorhydria in but 2 cases. Apparently achlorhydria is not any more frequent in colitis than in a similar group of normal individuals of the same age and sex.

Cardiovascular-renal Disease. Disease of the heart, kidneys or bloodvessels was noted in 35 cases (17 per cent), a normal incidence for patients in this age group. These cases were distributed as follows: arteriosclerosis 10 cases, hypertension 10 cases, nephritis 4 cases and heart disease 11 cases.

Chronic Arthritis. Faber[40] reported the presence of achylia in 15 of 65 cases of polyarthritis. In an analysis of 250 cases of arthritis, Miller and Smith[41] found achlorhydria and hypochlorhydria 5 times more frequently than in normal individuals. Lottrup[42] found that 44 per cent of his cases of chronic progressive polyarthritis had achylia. Chronic arthritis was noted in only 8 of 210 cases of achlorhydria in this series.

Dermatoses. In a survey of 12 cases of acne rosacea by Ryle and Barber,[43] achlorhydria was encountered 5 times and hypochlorhydria twice. Brown[44] analyzed 50 cases of acne rosacea and found achlorhydria in 7 and hypochlorhydria in 8 cases. We encountered only 1 case of acne rosacea and 3 of chronic eczema in the series.

Other Diseases. Not a single case of proven duodenal ulcer was noted in the series. There was, however, 1 case of gastric ulcer: it occurred in an untreated luetic negro with symptoms of only 1-year duration who was suspected of having carcinoma. At operation a large ulcer was found on the posterior wall of the stomach in the antrum. The pathologist failed to find evidence of cancer or any definite evidence pointing toward its luetic origin. This patient did not have a true achylia (enzymes present after histamin).

Gastrogenous Diarrhea. Diarrhea was present in 33 of 210 cases with achlorhydria. In 21 cases (10 per cent) other causes could be ruled out, and the diarrhea was apparently dependent upon the achlorhydria and responded to acid or gastritis therapy. True achylia was found in only 2 of the 21 cases. Gastrogenous diarrhea does not occur more frequently in association with true achylia than with achlorhydria. Only 1 of 15 cases of pernicious anemia had gastrogenous diarrhea. Six cases showed definite evidence of gastritis. Five patients were alcoholics. Gastrogenous diarrhea invariably responds to acid therapy. In 16 cases, which were followed, the diarrhea could be controlled but usually showed a tendency to recur if acid were stopped. It was found necessary to use as much as 8 cc. of dilute hydrochloric acid after each meal to control the diarrhea in some patients with alcoholic gastritis.

Gastric Evacuation Time in Achlorhydria. The time of gastric evacuation of the test meal was routinely recorded. Both clinicians and roentgenologists have noted a tendency toward rapid stomach emptying in achlorhydria. In 87 of 210 cases (41.4 per cent) the stomach emptied the test meal more rapidly than normal. Rapid gastric emptying was more common in true achylia (57 per cent as compared with 38 per cent in achlorhydria). The element of infection or of inflammation of the mucosa does not seem to be the factor

responsible for rapid gastric evacuation time, since only 41 per cent of cases with gastritis showed rapid emptying. Gastrogenous diarrhea did not occur more often in association with rapid stomach emptying (43 per cent) than in normally emptying stomachs. An observation of significance is the remarkable constancy of the rate of stomach emptying in the cases in which several gastric analyses were performed. Bell and MacAdam[45] found this to be true of normal individuals. Our study confirms this finding in patients with achlorhydria.

Constipation and Achlorhydria. Constipation was severe enough to be listed as one of the diagnoses in 71 of 210 cases of achlorhydria (34 per cent). It occurred 3½ times more often in achlorhydria than did gastrogenous diarrhea. It is unlikely, however, that the incidence of constipation is any more common in patients with achlorhydria than in other patients of similar age and sex. Constipation occurred just as frequently as gastrogenous diarrhea in the patient with rapid evacuation time. In 32 of the 71 cases of constipation the gastric emptying time of the test meal was too rapid.

Incidence of Focal Infection in 210 Cases of Achlorhydria. Obvious focal infection in the mouth was present in 98 of 210 cases (47 per cent). The foci were distributed as follows: teeth, 64 cases; tonsils, 41 cases; pyorrhea, 33 cases; and sinusitis, 8 cases. Foci of infection were found more frequently in association with gastritis (59 per cent as compared with 44 per cent). Since many of the cases of achylia and of true achlorhydria may have resulted from gastritis even though evidence of it cannot be obtained, the ablation of all foci of infection is undoubtedly important. The administration of hydrochloric acid in these cases takes on an added importance, at least until foci can be removed, as a prophylactic against the implantation of infection in the stomach and small bowel.

Summary. In a review of 210 cases of achlorhydria in patients with gastrointestinal complaints, it appears that the incidence of achlorhydria is greater in normal patients (in Vanzant's study, 12.1 per cent) than in patients who consult a physician for gastrointestinal complaints (5.7 per cent). It is more frequent in females and its incidence increases with age up to the seventh decade. No essential difference was found in the age incidence of true achylia and of achlorhydria.

The ordinary fractional gastric analysis is compared with the histamin gastric analysis in 64 cases. Forty per cent of cases of apparent achylia show either acid or enzyme secretion after histamin injection. Evidence is presented pointing toward the gradual development of secretory insufficiency; a complete permanent achylia probably does not occur suddenly.

The term "true achylia" should be used only when both hydrochloric acid and gastric ferments are absent throughout the period of a fractional gastric analysis which follows an injection of an ample

dose of physiologically potent histamin. The condition is practically always permanent. The status of gastric secretion as determined by histamin represents the maximum of gastric secretory work and can rarely be improved in spite of treatment of the underlying cause.

The significance and incidence of various diseases and symptoms which are commonly thought to be associated with achlorhydria are discussed. In 15 cases of *primary anemia* all had a true achylia; no return of acid after specific therapy was noted. We found no evidence of gastritis in any case and doubt if it is a frequent etiologic factor in the achylia of primary anemia. We feel that a true achylia gastrica is necessary to a diagnosis of Addisonian anemia.* In some cases at least the achylia precedes the development of anemia by many years. The achylia is probably the result of an inherited trait which does not manifest itself until later in life. The incidence of secondary anemia in our cases is considerably greater in true achylia than in achlorhydria.

Gastritis was noted in 19.5 per cent of the cases of achlorhydria. Foci of infection, alcohol, lues and cardiovascular-renal disease seemed to be of most importance in its etiology. In most cases of gastritis a secretory response follows repetition of the analysis after gastric lavage (Hurst) or histamin injection. Catarrhal duodenitis is a very frequent accompaniment of achlorhydria (50 per cent) but occurs more frequently if gastritis is also present (82 per cent).

We found *tertiary lues* more common in the cases of achlorhydria than its occurrence in a similar group of patients without achlorhydria. The significance of achlorhydria in gastric lues is discussed.

Carcinoma of the stomach was found in 16 cases. True achylia is rare, but achlorhydria is quite common in gastric cancer. The relationship which gastric acidity bears to the etiology of gastric cancer is discussed.

Contrary to prevalent opinion we found that the incidence of achlorhydria was no greater in cases of *gall-bladder disease* or *colitis* than it is in any group of individuals of the same age and sex.

The *constitutional asthentic habitus* of Stiller was present to some degree in 48 per cent of cases. The *habitus hypersthenicus* was so infrequent that its existence with achlorhydria should suggest a possibility of some underlying acquired pathologic condition.

Gastrogenous diarrhea occurred in 10 per cent of patients. It was not more frequent in association with achylia than with achlorhydria. Alcoholism and gastritis seemed to be factors of some importance in the production of the diarrhea.

Constipation was a major complaint in 34 per cent of cases, occurring 3½ times more often than diarrhea.

* This statement must be modified in view of Castle's recent reports. The so-called "specific stomach factor" may be absent in rare instances without there being an associated achylia. We have encountered 1 case of this type recently.

Rapid stomach emptying, present in 41 per cent of cases of achlorhydria, was decidedly more common in true achylia. Gastritis apparently was not a factor. When several analyses were carried out on the same patient, there was a remarkable constancy in the rate of stomach emptying. That rapid gastric evacuation *per se* is not the important cause of gastrogenous diarrhea is indicated by an equal frequency of rapid emptying in cases with constipation.

The incidence of foci of infection and the importance of their ablation in cases of achlorhydria is stressed.

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TRANSIENT COMPLETE BUNDLE-BRANCH BLOCK.

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The occurrence of bundle-branch block is fairly common, as electrocardiographic tracings have demonstrated. It is seen principally in patients with chronic heart disease and causes no characteristic symptomatology. King has described a reduplication of the apex thrust and a splitting of the first sound, by which its presence may be suspected, but the condition is recognized with certainty only through electrocardiographic records.

Complete bundle-branch block, coming on acutely in a patient without previous cardiac symptoms, has received scant notice in the literature. We have recently observed 2 patients in whom symptoms came on acutely, and in whom electrocardiographic tracings demonstrated a transient bundle-branch block.

Case Reports. Case 1.—Mrs. X, white, aged 46 years, was seen in consultation with Dr. Frank Conroy March 25, 1931, at 11.30 P.M. About 1 hour previously, while riding horse-back, she collapsed. There was expectoration of a pink frothy sputum. Physical examination showed bubbling râles throughout both lungs. The patient was in a state of shock. There was pallor and the skin was cold and moist. The right heart was dilated, the sounds weak, regular and clear. The blood pressure was 90 systolic and 58 diastolic. The patient was given morphin, $\frac{1}{6}$ grain and adrenalin (1 to 1000), 10 minims. The adrenalin was repeated twice before the patient was taken to the hospital at 1.30 A.M. By morning there were only a few râles present. The blood pressure had risen to 120 systolic and 76 diastolic. An electrocardiographic tracing (Fig. 1) showed a right* bundle-branch block. The symptoms cleared up completely within 48 hours. At no time was there pain or fever, and the leukocyte count was normal. A second electrocardiographic tracing 4 days later (Fig. 2) gave no evidence of bundle-branch block. The Wassermann test was negative, and the history gave no indication of lues. There had been no previous cardiac symptoms. There was no history of rheumatic fever. No evidence of thyroid disease was found. The clinical diagnosis was acute bundle-branch block, acute pulmonary edema. The physical signs over the heart did not suggest bundle-branch block.

Case 2.—The patient, a white female, aged 51 years, was admitted to the Surgical Service of the Cincinnati General Hospital, January 29, 1931, with the complaint of nausea, vomiting, and pain in the right upper quadrant of the abdomen. A mass was palpable in this region, and an explora-

* The usual conventional standards have been employed in identifying right bundle-branch block.

tory laparotomy performed. The mass was found to be a greatly scarred right lobe of the liver covered by a white thickened capsule. The gall bladder was obviously diseased, although containing no stones, and was removed, and the wound drained.

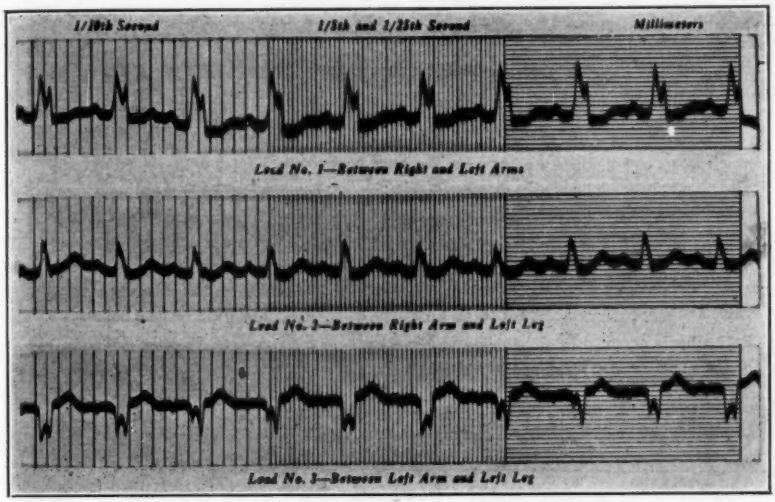
1/10th Second
1/5th and 1/25th Second
Millimeters
Lead No. 1—Between Right and Left Arms
Lead No. 2—Between Right Arm and Left Leg
Lead No. 3—Between Left Arm and Left Leg

FIG. 1

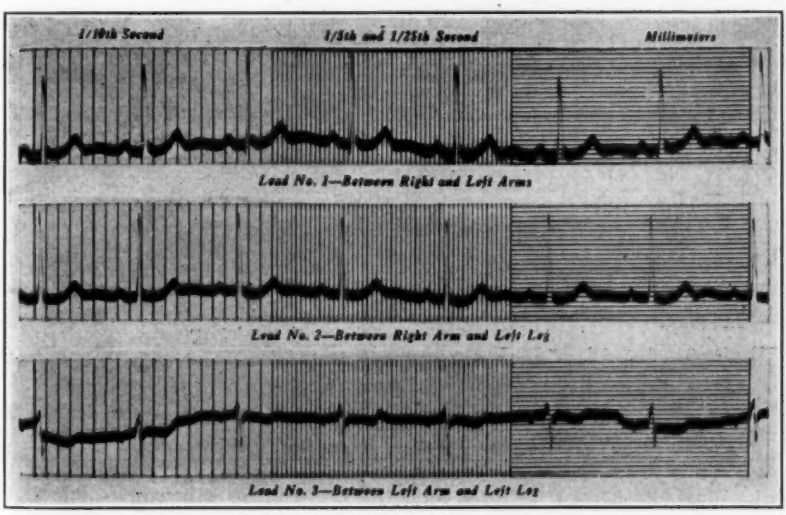
1/10th Second
1/5th and 1/25th Second
Millimeters
Lead No. 1—Between Right and Left Arms
Lead No. 2—Between Right Arm and Left Leg
Lead No. 3—Between Left Arm and Left Leg

FIG. 2

Convalescence was slow and complicated by some infection of the wound, a low-grade fever, and the development of ascites.

At this point it should be mentioned that on admission the heart showed nothing of interest except for a soft systolic murmur at the apex. There was a slight hypertension. The blood pressure was 158 systolic and 98

diastolic. Relative cardiac dullness was 3 by 9 cm. The pulse was regular. Laboratory data before and after operation were of no significance except for the presence of a positive blood Wassermann test.

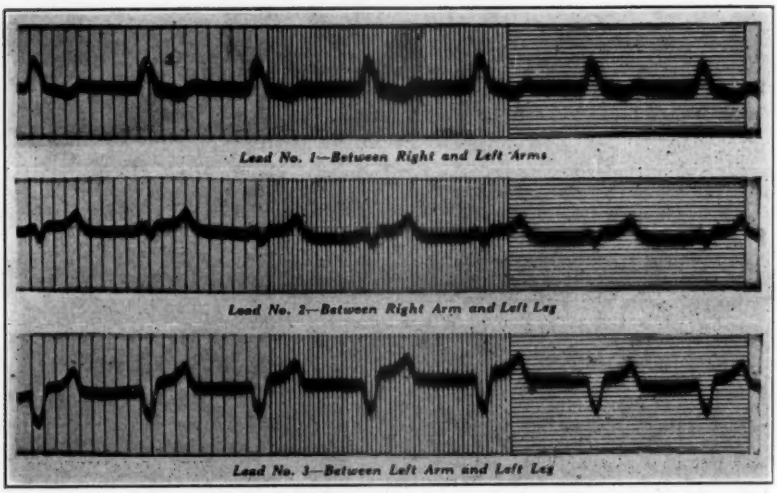

FIG. 3

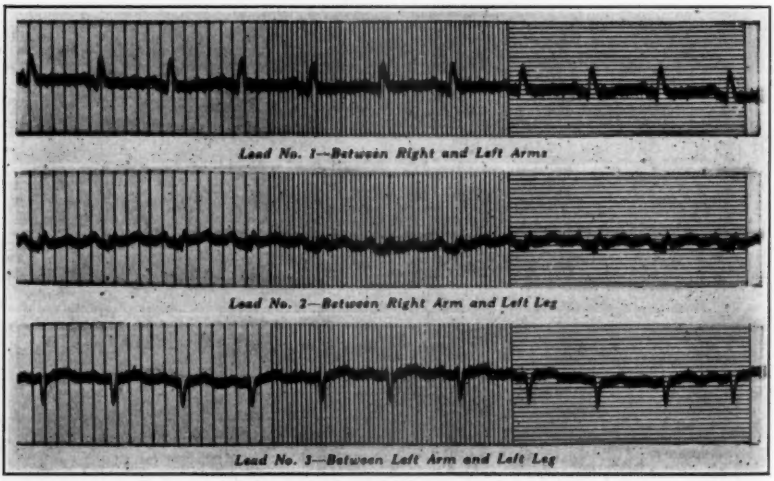

FIG. 4

On March 10, the pulse rate suddenly dropped from an average rate of 140 to 60, and simultaneously the patient went into a condition of shock. There was definite air hunger, slight cyanosis of the nail beds and lips, pallor, sweating, profound exhaustion, and a temperature of 95° F.

The pulse was regular, of low tension, the blood pressure 70 systolic and 40 diastolic, and the rate 68. The veins of the neck were somewhat distended and there was slight pretibial edema. There was no visible apical

impulse; percussion indicated slight enlargement to the left and right. No shock or thrill was noted. No gallop rhythm or splitting of the first heart sound was heard. A loud rough apical systolic murmur was present.

An electrocardiogram (Fig. 3) was taken at once which showed right bundle-branch block. No "*P*" waves were discernible, but there was no irregularity and the rate was only 70. Nodal rhythm (Type II) was suspected, and additional support for this impression was afforded by a record made with needle electrodes and thoracic leads, which showed neither "*P*" waves nor the oscillations associated with auricular fibrillation.

The usual treatment for shock was instituted—caffein, adrenalin, and small amounts of hypertonic glucose intravenously. Gradual improvement ensued, the symptoms of shock lasting only 3 days.

Subsequently there has been no marked general change for the better. Weakness, ascites, and some edema of the ankles continue to be present, and the liver has increased in size and is nodular and indurated.

However, rather significant alterations have appeared in the electrocardiogram. A record of April 20 (Fig. 4) showed disappearance of the bundle-branch block with restoration of normal sinus rhythm. There was, however, low voltage, slight widening and slurring of the "*Q–R–S*" complexes in all leads.

Discussion. Wolff, Parkinson and White report the occurrence of transient bundle-branch block associated with paroxysmal tachycardia in children and young adults.

In the cases reported in this paper, cardiac symptoms developed acutely in patients who had previously been free from circulatory disturbances. In one there was an acute pulmonary edema. This patient was apparently in perfect health. A few hours after the onset of the pulmonary edema, complete bundle-branch block was demonstrated. The symptoms cleared up completely, and the bundle-branch block disappeared. In our review of the literature, we have not seen *transient complete* bundle-branch block emphasized. That profound disturbances may be associated with it is shown by the occurrence of acute circulatory failure in the 2 cases reported. Willius and Keith report 2 similar cases of acute pulmonary edema with transient *incomplete* bundle-branch block.

What the nature of the lesion in the bundle-branch tissues may be is not at all clear. Whatever it is, it produces only temporary interference in the function of the conducting system. In Case 1, a complete study failed to reveal any evidence of organic disease, aside from the findings reported in the abstract. The absence of pain, fever, leukocytosis and friction rub, eliminate a coronary occlusion in our patients.

While we have no definite proof, we believe it reasonable to assume that the occurrence of acute symptoms coincided with the development of bundle-branch block.

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ARTERIOLAR STUDIES IN PATIENTS WITH HYPERTENSIVE HEART DISEASE WITHOUT HYPERTENSION.*

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The association of diffuse arteriolar sclerosis and essential hypertension can no longer be questioned. Numerous investigators[1,2,3] have definitely identified the histologic nature of the characteristic lesion in this disease and its widespread distribution throughout the body. Diffuse arteriolar sclerosis is pathognomonic of persistent hypertension. The arteriolar sclerotic or primary contracted kidney, for example, always evidences a present or previous hypertensive state.

Recently Kernohan, Anderson and Keith[4] have been able to demonstrate the same distinctive histologic changes in the arterioles of the voluntary muscles of ambulatory patients with diffuse hypertensive cardiovascular disease as are found at autopsy. After determining the ratio of wall to lumen in the vessel of normal individuals as a standard, the marked narrowing of the lumen of the arterioles in essential hypertension was shown quantitatively. They found that in the normal the average ratio of vessel wall to lumen is 1 to 2, with variations from 1 to 1.7 to 1 to 2.7, whereas the average ratio for the arterioles of the hypertensive patients was 1 to 1.4 in cases of benign hypertension and 1 to 1.1 in cases of severe benign and malignant hypertension.

It occurred to us that similar biopsy studies might be of confirmatory value in the diagnosis of a phase of cardiac disease which we designate "hypertensive heart disease without hypertension,"[5] although it is recognized that the ratios have only relative value on account of various uncontrolled variables in the preparation of the specimen. Not infrequently individuals are encountered who have cardiac enlargement with normal or low blood pressure but no organic valvular lesion, adhesive pericarditis, severe anemia or other recognized cause for the enlargement. Even though the former level of the blood pressure is unknown, convincing clinical or path-

* Read before the Central Society for Clinical Investigation, Chicago, Illinois, November 20, 1931.

ologic evidence of a preëxisting hypertension can always be found. Aside from the otherwise unexplained cardiac hypertrophy these patients may show impairment of renal function or even uremia, a suggestive roentgenologic cardiac silhouette, coronary types of electrocardiograms as are so often found in the known hypertensive individuals, ophthalmoscopic signs of known hypertension, and finally autopsy discloses diffuse arteriolar sclerosis which always evidences a persistent hypertension during the life of the individual.

Because of the normal or reduced pressure found when first examined, these patients frequently are classified wrongly. If an apical systolic murmur is present a diagnosis of mitral insufficiency is made. If a murmur at the base is heard some other valvular diagnosis follows, while if no murmur is audible the diagnosis may be "chronic myocarditis" or some other equally obscure entity. The American Heart Association[6] merely suggests that these persons be placed in the group of unknown etiology. The actual and alarming frequency of hypertensive states is undoubtedly obscured to a great degree because of such wrong classifications.

Our present study includes biopsies performed on 11 individuals with cardiac enlargement but normal blood pressure and no other factor to explain the cardiac enlargement. The method and histologic technique pursued was similar to that of Kernohan, Anderson and Keith[4] on the known hypertensive individuals. Under local anesthesia small pieces of the deltoid muscle were removed. These specimens were submitted to the pathologic laboratory along with controls but without the clinical histories, so that the findings should be unbiased.

Tissues were fixed in Zenker's fluid, embedded in paraffin, cut at 7 micra and stained with hematoxylin and eosin. Those showing various stages of thickening of the vessel walls were also stained with Mallory's connective-tissue stain and osmic acid.

Arterioles, vessels measuring from 30 to 100 micra in outside diameter and cut at right angles, were selected. Measurements were made with a Bausch & Lomb ocular micrometer. The wall and lumen of each vessel were measured twice at right angles and averaged. The ratio consists, then, of the average thickness of the wall found by measuring it four times at right angles to the average diameter of the lumen found by measuring it twice at right angles. Three to five arterioles were measured in each case.

A summary of the clinical and pathologic data is shown in the accompanying table. Some of the patients came to the medical out-patient department. The others were observed in the wards of the hospital. The ages ranged from 41 to 88 years. All gave a history of the anginal or congestive type of heart failure of many months' duration. Suggestive roentgenologic, electrocardiographic and ophthalmoscopic evidences of a preëxisting hypertension were present. Three of the patients died shortly after the biopsies were

TABLE 1.—ANALYSIS OF DATA OF 11 CASES WITH BIOPSY.

Pathology Lab. No.	Sex.	Race.	Age.	History.	Wassermann.	Blood pressure.	N.P. nitrogen.	Roentgen ray: cardiothoracic ratio.	Electrocardiogram.	Ophthalmoscopic picture.	Ratio of arteriolar wall to its lumen.
30-663	M.	White	76	Symptoms for 18 years, leads a very restricted life. Has dyspnea and substernal pain on exertion	Negative	120/85 mm. Hg.	27.9 mg. per 100 cc. blood	15.5:29 cm. Aorta widened	Auricular fibrillation; ventricular premature contractions; slurred *Q-R-S* and low voltage	Tortuosity and thickening of arterioles	1:0.95
30-670	M.	White	70	Symptoms for 4 years, leads a restricted life. Has dyspnea on exertion and edema of feet and ankles	Negative	120/76	35.4 mg.	18:28 cm. Marked cardiac enlargement	Bundle branch block	Negative	1:0.85
30-661	M.	Negro	56	Right hemiplegia 4 years ago. Symptoms of heart failure date back 18 months. Leads a restricted life	Negative	130/80	....	18.5:29.5 cm.	.....	....	1:1.02
30-782	M.	Negro	66	Dyspnea and edema of lower limbs began 18 months ago	Negative	144/70	30 mg.	17.5:32.5 cm.	Auricular fibrillation; slurred *Q-R-S* and low voltage in all leads	Slight sclerosis of arterioles	1:0.70
30-671	F.	White	65	Symptoms of congestive heart failure for 2½ years. Leads a very restricted life	Negative	140/60	31.5 mg.	14.5:23 cm.	Auricular premature contractions, T-I+ T-II inverted, slight slurring of *Q-R-S*	Disks blurred, sclerosis of arterioles	1:0.83
30-707	M.	Negro	41	Congestive heart failure for past 18 months. Left hospital slightly improved. Died suddenly a few weeks later	++++	120/70	35 mg.	17.5:26.5 cm. Aorta widened	.....	....	1:0.73
30-708	M.	Negro	73	Symptoms of congestive failure for past 18 months	++	118/82	31 mg.	15:28 cm. Aorta widened	T-II inverted, *Q-R-S* widened in all leads	Arterioles tortuous	1:1.31
30-747	M.	Negro	88	Weakness and dyspnea for past several years. Edema of lower limbs. Recently substernal pain and nocturnal dyspnea. See autopsy report	Negative	130/80	57 mg.	20:28 cm. Aorta markedly widened	.....	Disks pale, arterioles tortuous	1:0.96
30-662	M.	Negro	52	Congestive failure for past year	Negative	130/86	26 mg.	15:27.5 cm.	T-I flattened, T-II isoelectric, deep Q-III, LAD.	Negative	1:1.23
30-832	M.	Negro	54	Dyspnea and edema for past 6 months	a/c	110/70	26 mg.	19:30 cm.	Low voltage, T-I isoelectric	Arterioles very tortuous	1:1.05
30-781	M.	Negro	50	Repeated admissions for congestive heart failure during past 4 years. Dead	++++	98/90	50 mg.	16:29.5 cm.	Low voltage and slurring of *Q-R-S* in all leads	Arterioles very tortuous and thickened	1:0.88

performed. Only one autopsy was obtained. The ratio of wall to lumen in the cases ranged from 1 to 1.31 to 1 to 0.70. This corresponds to the average ratio of 1 to 1.4 to 1 to 1.1 found by Kernohan, Anderson and Keith[4] in the known hypertensive individuals and is in marked contrast with the ratio of 1 to 2 found by them in normal controls and informally confirmed by us.

Pathology. The histologic changes were very similar to those described by Kernohan, Anderson and Keith in the known hypertensive patients. In most of the cases there were some changes in the skeletal muscle consisting of degeneration of the sarcoplasm. The sections showed occasional isolated muscle cells in which the cytoplasm was entirely granular, there being a loss both of the longitudinal and cross striations, and a loss in the staining power of the nuclei. Most of the specimens showed some fibrosis about the arterioles. This appeared more marked in those cases in which the normal wall-lumen ratio was most reduced. There was little lymphocytic infiltration in this fibrous tissue.

Studies of the arteriole walls showed the most characteristic and prominent change to be in the media. This change was evidenced by an increase in thickness of the media, and by an increase in the number of nuclei on cross-section. The muscle cells appeared to be increased in size, though this could not be proved with certainty. There was also definite thickening of the intima in all of the cases. This intimal thickening was less marked in those vessels showing the least disturbance of the normal wall-lumen ratio. The increased thickness of the intima was characterized chiefly by an increase in the internal elastic lamina. In the normal arteriole the internal elastic lamina is scarcely visible, but in the sections studied there was a definite thickening of this layer as shown by Mallory's connective-tissue stain. In our series there appeared to be very little, if any, proliferation of the lining endothelial cells. Studies of the tissues stained for fat with osmic acid failed to show any lipoid infiltration. There was no evidence of deposition of calcium or processes of degeneration in the media in any of the sections.

The following case history and necropsy is illustrative of the clinical and pathologic findings in a patient with "hypertensive heart disease without hypertension:"

Case Report No. S 30-747.—Male, negro, aged 88 years, was admitted to the Louisville City Hospital on October 16, 1930, complaining of weakness and dyspnea of several years' duration. There had been progressive edema of the dependent portions of the body. During recent months attacks of nonradiating substernal pain were experienced and also frequent paroxysms of nocturnal dyspnea. Neither the family history nor that of previous illnesses was of importance.

Examination revealed an undernourished, senile, orthopneic negro whose palpable arteries were sclerosed and tortuous. The blood pressure was 130 systolic and 80 diastolic mm. Hg with the heart markedly enlarged. There was a loud blowing apical systolic murmur and a totally irregular

rhythm. A flat percussion note was present over the right lung base posteriorly but the voice and breath sounds were not dependable because the patient could not coöperate. The liver was palpable 3 cm. below the right costal margin.

Roentgen ray examination confirmed the fact that marked cardiac enlargement was present. The urine contained albumin but was negative for glucose. His hemoglobin was 65 per cent, with 3,000,000 erythrocytes, 10,000 leukocytes and nothing unusual in the stained film. The ophthalmoscopic examination revealed abnormally pale disks, tortuous arterioles but no hemorrhages. The blood Wassermann was negative.

The blood chemical studies revealed the following findings:

Date.	Nonprotein nitrogen.	Urea nitrogen.	Creatinin.
October 17, 1930 . . .	57 mg.	30 mg.	2.4 mg.
October 21, 1930 . . .	44.4 mg.	24.0 mg.	2.5 mg.
October 24, 1930 . . .	56.4 mg.	28.5 mg.	2.7 mg.

Two days following admittance he was more dyspneic and his blood pressure was 138 systolic and 94 diastolic mm. Hg. Two days later auricular fibrillation was still present and he had a marked Cheyne-Stokes type of respiration. On October 21, 1930, a specimen of the deltoid muscle was obtained and sent to the pathologist. His blood pressure could not then be obtained with certainty. The edema was approximately the same as on admission, although he had been digitalized, placed on a restricted diet with limited fluids and received various diuretics. Because of his restlessness and inability to coöperate it was impossible to secure an electrocardiogram.

He died suddenly 2 weeks after admission to the hospital.

Necropsy. The necropsy was limited to the thoracic and abdominal cavities. The pericardial sac contained the usual amount of fluid and the heart weighed 570 gm. Organized thrombi were found in both atrii. There was hypertrophy of the musculature, particularly of the left ventricle, which measured 2.5 cm. in the thickest portion. At the apex there was some hemorrhage into and softening of the myocardium with fibrosis of the papillary muscles. The aortic cusps were thickened and a moderate calcification of the aorta itself was present. Moderate sclerosis of the coronaries was visible, though careful search failed to reveal a gross thrombosis.

The liver weighed 1100 gm., was firm and the cut surface showed a yellowish mottling. Nothing of interest was found in the lungs and the gastrointestinal tract was not remarkable except for varicosities of the esophageal and rectal veins.

The right kidney weighed 150 gm. and there was a large yellowish, necrotic area on the posterior surface. In the remaining portion of this kidney there were a few old indentations which were interpreted as healed infarcts. The left kidney weighed 130 gm. and was studded with similar old indentations. Over these areas in both kidneys the capsule was adherent. On section these indentations extended well down toward the pelvis and appeared to be composed of scar tissue. The cortex and medulla were fairly well differentiated though the cortex was thinner than usual.

Microscopic Examination. Sections of the heart showed generalized enlargement of the muscle cells with some evidence of degeneration. In the cytoplasm of many of the cells there was a slight amount of brown pigment. There were a few small scars in the stroma which extended out into the muscle bundles and in these areas some of the muscle cells had undergone necrobiosis. The small vessels were fairly well preserved though in most of them the lumen appeared to be definitely narrowed. Section through the apical portion showed some of the smaller branches of the coronaries to be thrombosed.

The lungs showed "heart failure" cells and thickening of the walls of the air sacs. There was evidence of an early bronchopneumonia.

The liver showed a picture of chronic passive congestion as well as many petechiæ. The arterioles were definitely narrowed.

The sections of the kidney showed considerable damage to the kidney substance by small infarcted areas. Associated with these were thickened vessels, the lumen of some being entirely closed. Sclerosis of the capillary tufts was evident. A slight degree of acute degeneration of the tubule epithelium was noticeable, though most of the epithelium appeared atrophic. In one of the sections there was a recent infarct in which the kidney substance was in an early stage of coagulation necrosis but unfortunately the occluded vessel itself was not in the section.

Measurements of the arterioles of the skeletal muscles showed a wall-lumen ratio of 1 to 0.93, which compared favorably with that in the biopsy. The wall-lumen ratio of the arterioles in the other organs was as follows: heart, 1 to 1.20; liver, 1 to 1.03; pancreas, 1 to 1.2; spleen, 1 to 0.83 and kidney, 1 to 0.87.

Discussion. All of our cases with cardiac enlargement but normal blood pressure and no recognized factor to explain the cardiac enlargement showed arteriolar changes characteristic of known hypertension. Thus biopsy studies are of definite confirmatory value in the diagnosis of "hypertensive heart disease without hypertension."

Such an examination is not a necessary routine. A diagnosis of a preëxisting hypertension can be made on the basis of the cardiac enlargement alone. Geoffrey Evans[2] concluded that cardiac hypertrophy without organic valvular lesion or chronic pulmonary disease found postmortem is good evidence of a raised blood pressure during life. Ophüls[7] called attention to the fact that preëxisting hypertension could explain the cardiac hypertrophy in such cases as described above. He merely states in referring to a clinical study of such cases by Christian[8] that "his patients must have suffered from continued hypertension at one time or another, because with the exception of valvular lesions—which were not present—this is the only condition which can reasonably explain the hypertrophy of the left side of the heart—which was said to have been present." Again, in a later study, Ophüls[9] says, "The presence of cardiac hypertrophy in these cases has been regarded by us as evidence of the previous existence of high blood pressure for a sufficient period of time to produce such hypertrophy." Cabot,[10] in a pathologic study, includes in the classification of hypertensive cardiovascular disease "all necropsied cases showing a hypertrophied and dilated heart associated with nephritis, with arteriosclerosis, with both or with neither, but without valvular disease, chronic pericarditis and any other recognized cause of cardiac enlargement." Bell and Clawson[11] state that a diagnosis of primary hypertension may be made clinically "in a person suffering from chronic cardiac disease, with low or normal pressure, if there is a demonstrable cardiac hypertrophy of the left ventricular type not associated with any disease known to cause hypertrophy."

It seems unnecessary to cite many references to the valuable evidence of hypertensive states obtained by ophthalmoscopic exam-

ination. When retinal changes once occur they persist as mute evidence of arterial hypertension, regardless of whether the pressure remains high or falls to subnormal levels. O'Hare and Walker[12] have shown that "the finding of retinal arteriosclerosis in patients with a normal or low blood pressure probably indicates the existence of a previous hypertension with subsequent myocardial weakening or loss of vascular tonus." Retinal changes alone may be sufficient for a diagnosis of hypertensive heart disease.

Master[13] described the "high-voltage electrocardiogram" and the "hypertension roentgenogram" and claimed that they may be the only existing evidence of a previously long-standing hypertension. O'Hare, Calhoun and Altnow[14] state that 81 per cent of their cases of "chronic myocarditis" with low blood pressure and characteristic retinal changes had typical or suggestive roentgenograms of the hypertensive heart.

Should it be impossible to make with certainty an antemortem diagnosis of a preëxisting hypertension from the cardiac enlargement, retinal findings, the electrocardiogram or the Roentgen ray, a biopsy may be performed. It permits an immediate diagnosis instead of a postponement of the diagnosis until autopsy findings are disclosed.

Arteriolar lesions were found in the deltoid muscle of all our cases. The frequency with which arteriolar lesions of the voluntary muscles was found by Kernohan, Anderson and Keith is far greater than that reported in the work of others. They comment on this and offer the possible explanation that previous investigators, perhaps, did not include cases of the serious progressive type of hypertension, such as those which they classed as cases of early malignant or malignant hypertension. More recently Barker, Keith and Kernohan,[15] from a study of specimens obtained at biopsy from the pectoralis major muscle in more than 100 cases of hypertension have confirmed this work of Kernohan, Anderson and Keith. None of our biopsy cases had malignant hypertension. It is probable that marked and characteristic arteriolar lesions were found in every instance by us because our cases were "worn out" hypertensives. They undoubtedly had hypertension over a long period of time before coronary changes or myocardial failure reduced the level of the blood pressure.

Summary. 1. Biopsy specimens of the deltoid muscle were obtained from 11 individuals with cardiac enlargement but normal blood pressure and no other factor to explain the enlargement.

2. Histologic changes in the intima and media of the arterioles similar to those encountered in known hypertensives were found in all.

3. Careful measurements of the arterioles of the specimens gave a ratio of wall to lumen from 1 to 1.31 to 1 to 0.70, similar to ratios found in known hypertensives and in marked contrast to the normal ratio of 1 to 2.

4. Three patients are now dead and one autopsy was obtained in which a generalized arteriolar sclerosis was found.

5. The frequency with which hypertensives show arteriolar lesions of the voluntary muscles is discussed.

6. A diagnosis of "hypertensive heart disease without hypertension" may be confirmed by biopsy studies of the voluntary muscles.

NOTE.—We desire to express our sincere thanks to Dr. John Walker Moore, Dean, for his kind permission to make this study; to Dr. A. James Miller head of the Department of Pathology, for valuable suggestions and technical assistance; and to the resident staff, both medical and surgical, of the Louisville City Hospital for their interest and assistance.

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COMBINED TAPE-MEASURE AND STETHOSCOPE TUBE.

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A SHORT flexible tape-measure is a necessary item in the armamentarium of the physician who attempts to achieve accuracy and precision in the field of physical diagnosis. Because of the frequency

with which such an instrument is forgotten, mislaid or lost, the average physician usually relies on his ability correctly to gauge

The tubing is manufactured by the Orsell Company, 108 West 78th Street, New York City.

certain measurements during the course of his examination of patients. Others, however, have attempted to obviate the difficulty by combining a readily available measuring tape with the stethoscope. This has been done by calibrating one of the rubber tubes of the stethoscope with ink, or by cutting notches in the rubber at measured intervals, with not entirely satisfactory results from the standpoint either of accuracy or durability of the markings.

Some time ago, while interested in the development of calibrated surgical drainage material, the idea of using the same method to calibrate stethoscope tubes occurred to us. An immediate trial convinced us of its value but disclosed one serious objection, namely, the inadvertent stretching of the tubing by the examiner while taking measurements. This objection was, however, readily overcome by a method of construction which we shall describe later.

The tubing is constructed in the following manner: Calibrations, 0.5 cm. apart, are vulcanized directly on a very thin strip of white rubber, 4 mm. wide, which constitutes the background. This calibrated rubber strip, in turn, is vulcanized and processed directly to the rubber tubing. The entire unit is then coated with a very thin layer of rubber, which imparts to it a smooth finish. Thus the calibrations which are now an integral part of the tubing are of permanent character and do not fade when subjected to hard usage, boiling, or chemical sterilization. Stretching of the tubing is prevented by incorporating several strong linen threads within its substance at the time of manufacture. This in no way interferes with its flexibility but merely prevents it from stretching. The calibrated strip begins at a point about 3 cm. from the distal end of the tube so that the portion immediately adjacent to the bell of the stethoscope is blank and enables one to hold the end of the tube without obscuring the calibrations.

We have found this simple device to be entirely adequate in accurately measuring the distances from the right and left cardiac borders to the sternum, the width of mediastinal dullness, the circumferences of various parts, etc. Undoubtedly other practical applications will suggest themselves.

THE CHANGES PRODUCED IN THE BLOOD PICTURE BY REMOVAL OF THE NORMAL MAMMALIAN SPLEEN.*

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The effects on the blood picture of removal of the normal spleen have remained a subject of dispute in spite of the apparently simple nature of the problem and of the many studies that have been made upon it over more than a half century. While, for instance, the

* This article is also to appear in the Libman Memorial Volume and in Le Sang in a French translation.

majority believes that the spleen, in addition to its blood destroying function, has a stimulating effect on red blood cell formation (as evidenced by the anemia that follows its removal); others, chiefly German writers, have actively supported the view that the spleen normally inhibits red blood cell formation.

Difficulties Involved in This Problem. Though the reasons for this discord are not entirely clear, certain factors undoubtedly contribute, which have rarely received adequate consideration. In the first place the spleen, though accepted as an important member of the hemolytopoietic system, is one of the most variable of the viscera in size and weight in relation to general body weight, both at different stages of the individual's existence, and in different individuals of the same species, and in different species. In rabbits, for instance, it averages about 0.05 per cent of the body weight whereas in man, dogs and monkeys this ratio is more in the neighborhood of 0.25 per cent. It is therefore obvious that removal of the rabbit's spleen can hardly be expected to give as characteristic a light on the absent function as in the other cases; and yet negative results on this animal (a notoriously unsatisfactory subject for hematological investigations anyhow) have frequently served to cloud this issue. In Wade Brown's[1] studies on constitutional variation and susceptibility to disease, the spleen proved to be one of the most variable of the organs, and its gradual shrinkage with increasing age is a well-known occurrence. Study of splenic function has always been hampered by the double fact that, first, as a ductless organ, its action must usually be studied in a negative way, by the changes brought about by its removal, and yet, second, the effects of this removal, only eliminating one member of the reticuloendothelial system, are soon masked by the compensating effects of other members of the system, especially bone marrow, liver and lymph nodes. While the changes following removal are more easily demonstrable on the hemolytic side (phagocytosis, hemosiderin, etc.), the hemopoietic shifts after splenectomy—especially those of a regulatory nature—are more difficult to determine. Even with such cytological evidence as the bone marrow hyperplasia that eventually follows splenectomy, it is difficult to evaluate how much of this is a true increase of hemopoietic tissue and how much is connected with the newly increased function of blood cell destruction. An extreme example of this type of difficulty is found in studies of spenectomy in lower orders. For instance, in the salamander the spleen is the chief organ of erythrocytopoiesis (Jordan and Speidel[2]); and yet after its removal new erythrocytes apparently can be differentiated in the general circulation as well as in the heart and liver sinuses.

Another source of confusion has been the tendency—so often present in biologic investigations—to base conclusions on too small a series of animals or on subjects studied over too short a period.

Where the change sought for is sure not to be marked, as is obvious from the long-continued disagreement, a large number of test subjects obviously becomes the more necessary. An adequate period of observation is necessitated not only to get past the ordinary effects of anesthesia and a major surgical operation, but also because the characteristic spleen effects are not best observed for a few weeks and not concluded until often many weeks after removal of the organ. And yet some of the experimental studies which led toward the use of splenectomy in pernicious anemia some 20 years ago, for instance, were limited to only two or three animals observed for 1 or 2 weeks after splenectomy. For similar reasons, the most careful controls are especially necessary. The importance of such details as use of the same instruments by the same person under identical conditions at the same time of day, reduction of technical error and emotional excitement in the test animals to a minimum, adequate pre-operative examinations and preparations to establish a true base line, has only been appreciated by us after years of acquaintance with the problem and, as might be expected, is often missed in the published reports. Not only are the normal variations in hemoglobin and red cell counts far greater than was earlier appreciated (*cp.*, L. Pearce's[3] Study of the Blood Cytology of the Rabbit) but also seasonal variations (Platt and Freeman[4]) and emotion (Lamson,[5] and Cannon and Izquierdo[6]) are known to play a not inconsiderable part.

Still further confusion has been caused by using the changes found after therapeutic removal of a pathological spleen in various anemias as throwing light on the relation of the normal spleen to blood formation and destruction. Not only is this *ipso facto* a faulty procedure in general, but also in the case of the spleen, the diseased organ is known often to be a site of greatly increased blood destruction. Removal of a diseased organ, therefore, would tend on general grounds to lessen an anemia, and also in this case the removal of a hyperactive blood destroying factor would raise the blood level, irrespective of the normal organ's effect on blood formation. Thus two of the chief supports for the view that the spleen has an inhibiting effect on red blood cell formation can be shown to be vulnerable to destructive criticism.

Legitimate differences in interpretation also play their rôle. Thus recently Chiatellino and Goldberger[7] report that three splenectomized dogs showed a much greater rise of hemoglobin and erythrocytes when taken to high altitudes than did 3 controls, on account of the absence of the so-called inhibitory effect of the spleen. The protocols, however, show that the splenectomized dogs started anemic (4.9, 5.0 and 4.7 million reds *vs.* 8.0, 7.3, 5.4 respectively of the controls) and therefore had a greater demand for an erythrocytic increase. One is naturally curious also to know why the splenectomized animals were anemic before being taken to high altitudes! The data of other (*e. g.*, Roese[8]) are so inadequately presented that deductions are difficult.

TABLE 1.—THE LITERATURE ON THE ERYTHROCYTE COUNT AFTER SPLENECTOMY.*

For Appearance of Anemia.

Bathias[12]: (rabbits for 2 to 4 weeks).
Bittner[13]: (rabbits, slight, inconstant).
Bizzozero and Salvioli[14]: (g. pigs, dogs).
Bucalossi[15]: (reference not available).
Catellani[16]: (man).
Darling[17]: (man).
Eddy[18]
Emilianow[19]: (dogs).
Fowler[20]: (man).
Freytag[21]: (rabbits, slight, 2 weeks).
Gibson[22]: (dogs, maximum 60th day).
Godard and Palios[23]: (g. pigs, normal in 4 to 6 weeks).
Grigorescu[24]: (man and dogs).
Hartmann and Vaquez[25]: (several human cases).
Hirschfeld and Fabisch[26]: (16 rabbits, drop then rise).
Hitzrot[27]: (man, majority of cases).
Istomanowa, *et al.*[28]: (dogs, confirm *all* our findings).
Jepson[29]: (man, drop of 1.7 mill. on first day).
Johnstone[30]: (dogs).
Keller[31]: (g. pigs, slight for 10 days).
Krumbhaar and Musser[32]: (monkeys, slight).
Laudenbach[33]: (dogs, 4 days to 4 mos.).
Levi[34]: (rabbits, 14 per cent).
Loesch, *et al.*[35]: (dogs).
Maggioriani[36]
Malassez and Picard[37]: (3 dogs, Hb. even lower).
Matthews and Miles[38]: (man, long slight drop though authors conclude that reds behaved normally).
McCoy[39]: (man).
Meyers[40]: (boy).
Mole[41]: (rabbits, first marked drop, then overswing in 8 to 65 days).
Mosler[42]: (dogs).
Musser[43]: (man, splenectomy for cyst, protracted drop).
Musser and Krumbhaar[44]: (dogs).
Nicolas and Dumoulin[45]: (dogs).
Noguchi[46]: (man).
Orr[47]: (rabbits, 60 days).
Pfeiffer and Smyth[48]: (man, still anemic 2 to 4 years later).
Pugliese and Luzzatti[49]
Roughton, Legg and Emery[50] (man).
Schindeler[51]: (reference not available).
Schulze[52]: (man).
Silvestri[53]: (dogs).
Sorge[54]: (mice and rats, drop up to 60 per cent, slight polyglobulia in 3 weeks).
Staehelin[55]: (man).
Swain[56]: (man).
Takagi[57]: (dogs).
Tauber[58]: (15 different animals).
Troilo[59]: (g. pigs, months).
Viale[60]: (reference not available).
Vulpius[61]: (goats and rabbits for 1 month).
Warthin[62]: (sheep, goats).
Weicksel and Gebhardt[63]: (dogs, quick anemia and no quick rise; dogs back to normal in year).
Winogradow[64]: (dogs, drop followed by hyperplasia in 150 to 200 days)
Wlaeff[65]: (man, splenectomy for cyst, maximum drop on 25th day; normal in 6 months).
Zesas[66]: (man and various animals).

Against Fall in Erythrocytes.

Asher and Du Bois[67]: (3 rabbits, decrease very slight if associated with thyroid).
Asher and Sollberger[68]: (rabbit, and short period. Slight if fed iron).
Asher and Vogel[69]: (rise in dogs).
Azzurini and Massart[70]: (4 dogs, 15 months; slight rise 1 to 3 days).
Bachman and Hultgren[71]: (rabbits, no details; only followed a few days).
Gabbi[72]: (rabbits, neutral; g. pigs, rise).
Heaton[73]: (man, no change).
Hirschfeld and Weinert[74]: (man, rabbits).
Huygebaert[75]: (no change in dog).
Kreuter[76]: (9 monkeys, show slight drop 9 weeks after).
Paton, *et al.*[77]: (dog, cat, rabbit. "No change" but some showed our mild anemia).
Ponticaccia[78]: (rabbits, rise; reference not available).
Port[79]: (rabbits, no change).
Pouchet[80]: (dog, cat, bird, triton, fish; no change, no counts given).
Roese[8]: (dogs and rabbits, short drop followed by rise, no pre-operative figures).
Schiff[81]: (neutral and rise; reference not found).
Schwunert and Krzywanek[82]: (dog, no drop while resting).
Shelley[83]: (2 cases of trauma, first had no counts between the 18th and 180th days, the second showed a distinct anemia from the 3d to 12th month of observation; neither had counts before the injury).
Tizzoni and Fileti[84]: (reference not available).
Zanda[85]: (dog).

* In parentheses are found indications of the species involved and occasional details about the change.

It is proposed now to examine the evidence concerning the effect of removal of the normal spleen, chiefly in dogs, rabbits, guinea-pigs and man, on the level of erythrocyte count, hemoglobin, reticulocyte percentage, fragility of erythrocytes and blood platelet count. On account of the infectious anemia (Bartonella) lit up by splenectomy in rats (Lauda[9]) this animal is not included, though evidence points toward development of a transient anemia even in rats free of this infection. The leukocyte changes (enduring leukocytosis with tardy lymphocytosis and eosinophilia) have been sufficiently discussed elsewhere.

The Effect of Splenectomy on the Erythrocyte Count. The point that has received the most attention, at first glance one of the simplest yet provoking the most contradiction, is the level of the erythrocyte and hemoglobin counts. As the reports are too numerous to be considered *seriatim*, the accompanying table of reported changes in the erythrocyte count has been prepared, though it is obvious that many minor variations are thus necessarily omitted. As the hemoglobin change is generally recognized as not significantly different, it can well be omitted; its consideration is also complicated by the exchange with muscle hemoglobin (Whipple, *et al.*[10]) and Ray's[11] observation that after splenectomy, the oxygen capacity of the erythrocytes decreased more rapidly than did the pigment, *i. e.*, that a nonfunctioning hemoglobin had also to be taken into account.

From Table 1 it is seen that the majority of investigations has found a significant anemia developing after splenectomy, but that a not inconsiderable number has found either no significant change or an actual rise of erythrocytes. Most of those finding an anemia have, like ourselves, found it beginning to develop shortly after operation, reaching a maximum in a few weeks and disappearing after several more. Hirschfeld,[86] however, who earlier[26] failed to find any anemia, has recently reported an initial, short anemia in experimental animals followed by polyglobulia at a time when others found the anemia developing or near its maximum. Roese,[8] of the same school of thought, reported similar changes—the explanation being that the early drop is connected with the loss of the spleen's iron-regulatory function, while the later rise is due to the loss of the spleen's inhibitory influence on bone-marrow hematopoiesis. Some of those finding the slower developing anemia, have found a polyglobulia (*e. g.*, Winogradow,[64] and occasionally ourselves), for which an overcompensatory mechanism has been suggested as a possibility, but where unassociated chance changes in general condition cannot be definitely ruled out. Where no anemia has been found, the spleen was thought to be indifferent toward blood formation; the suggestion has been made by those finding an anemia that possibly accessory spleens have been overlooked at operation in such cases, though in the later reports this item has usually been covered. It is but fair to add, too, that many of the articles

* In parentheses are found indications of the species involved and occasional details about the change.

reporting anemia are from an early period when the precautions I have previously referred to were least followed; and while many—perhaps most—of those failing to find a postsplenectomy anemia should be similarly discounted, there are a few that remain difficult to reconcile. The studies of Azzurini and Massart,[70] for instance, though on a small number of dogs, bear intrinsic evidence of such thoroughness that it is impossible for the advocates of postsplenectomy anemia to disregard them. The mild anemia of some of our own dogs, too, suggest that the spleen's influence is not of such intensity that its absence is *always* clearly manifested by present methods.

Our own studies, which have now continued at intervals over 21 years, have accumulated evidence on 32 dogs and 6 monkeys, sufficiently uncomplicated by other experiments such as bleeding, administration of oleate, hemolytic serum, etc., to throw light on the effect of absence of the spleen *per se*. All have shown anemia, the red blood cell count dropping on an average of 1.49 million cells per c.mm. (extremes 0.5 to 3.5 million) with similar falls in hemoglobin. Occasional blood-volume studies tend to show that this is a true diminution in number and not a change in concentration. Not only is the drop much more variable than in the first series reported by us, but the time of onset and duration have, as would be expected, shown considerably more variation. In the whole series, anemia was found to extend from the first to the 70th day after splenectomy (extremes) and reached its maximum, on the average, on the 29th day. (Extremes of maximum anemia fell between the 5th and 60th days.) The intact control dogs examined over long periods showed hardly more than the variations of the method's error (3 to 4 hundred thousand), if kept in good condition free from infection. The fact that these are less than the "normal" variations above referred to tends to show that observance of strictly standard conditions, especially the successful avoidance of emotional changes, minimizes normal variation. The controls on which such operations as partial hysterectomy, omentectomy, lymphadenectomy and unilateral nephrectomy were performed, sometimes showed an anemia comparable to the milder splenectomy anemias, but it reached its maximum at a significantly earlier point (2 to 14 days) and made a quicker recovery. While requiring consideration, therefore, it seems proper to regard these as nonspecific reactions separable from true splenic effects. In our monkeys, on the other hand, the slighter anemia reached its maximum on the 9th day after splenectomy and it might well be that other animals would reach a maximum still earlier. Not only must general species differences here be taken into account, but also the shorter natural duration of life in the smaller laboratory animals. It is worth noting that in Table 1 Kreuter,[76] the only other observer of the postsplenectomy blood changes in monkeys, is listed on his own interpretations as against

the development of anemia, though analysis of his figures showed a slight anemia that was very little less than that observed by us.

In recent years we have paid especial attention to the immediate postoperative changes in the blood pictures on account of the transient rise reported by some observers at this time. In 17 of our dogs such a rise was found (0.2 to 1.2 million cells per c.mm.) lasting from 1 to 3 days; but similar rises were also found in most of the controls. Attempts to evaluate by blood volume studies the factor of postoperative anhydremia in this change have thus far not given consistent results, but are still being continued. Loesch, Witts and Zimmermann[35] state that the severity of the anemia is masked by an oligemia, as shown by their blood volume determinations, and that the total amount of circulating hemoglobin may be reduced to one-third. It was also hoped that study of the reticulocyte* percentage as a sign of erythropoietic activity might throw light on the nature of this frequently observed rise. Six of 8 recently splenectomized dogs showed a rise in the reticulocyte percentage from a preoperative average of 0.3 per cent to 1.2 per cent 1 and 2 days after operation—slight, to be sure, as compared with the high values obtained in disease, but large when compared to our experience with normal dogs. Of 6 controls, 3 intact animals varied between 0.01 and 0.3 per cent reticulocytes (*i. e.*, normal) over considerable periods up to 19 months, while 2 undergoing unilateral nephrectomy showed no operative rise. While such evidence is based on far too few animals to be conclusive, and while it is impossible to rule out nonspecific postoperative effects, nevertheless it tends to indicate that splenectomy has a tendency in the dog to be followed for a few days by an increased number of reticulocytes in the peripheral blood. In the monkey Krumbhaar and Musser[32] failed to find any signs of regeneration in the peripheral blood, either of blasts or reticulocytes, which were actually diminished. Whether such an increase indicates increased bone marrow activity with an overflow into the blood or whether it is a sign of decreased maturing ability of the bone marrow with consequent delivery of immature cells to the blood stream is a matter requiring further investigation. Just as in the liver treatment of pernicious anemia the beneficent effect is shown first by an increase of reticulocytes (relatively more mature than the megaloblasts) and next by an increase of the still more mature normocytes, so here the converse is possible, that the increase in reticulocytes (if not accompanied by a true increase in the total number of erythrocytes) might be looked upon as a sign of interference with their normal maturation rather than of true increased erythropoiesis.

The Effect of Splenectomy on the "Fragility" of Erythrocytes. This is one of the few phases of this problem in which there is sub-

* This term, proposed by me (J. Lab. and Clin. Med., 1922–1923, **8**, 11) to indicate those immature erythrocytes which exhibit a reticulum after vital staining, should not be confused with the reticular cells of the reticuloendothelial system.

stantial unanimity. Whether the spleen is removed from normal animals or therapeutically in disease, there is always an increase of the resistance of erythrocytes to hypotonic salt solution, as well as to most other forms of damage. This has proved of clinical importance in hemolytic jaundice, where splenectomy brings the fragile cells to a point nearer normal resistance. This fact, coupled with observations that blood cells emerging from the spleen appear to be less resistant than the entering blood cells, indicates that the spleen has a hemocatatonistic (weakening) effect on certain (probably the effete) erythrocytes (Bottazzi[87]). While the great majority of investigators has found such an increase (we, for instance, having found it constantly in man, monkey and dog), only four investigators (as Lauda[9] points out in his review) have had contrary results. Frenckell and Nekludon,[88] who have found a constant hypercholesterolemia after splenectomy in dogs, cats and rats, think this to be the cause of the increased resistance.

Immature Erythrocytes in the Circulation after Splenectomy. A number of investigators have reported showers of Jolly bodies, or more rarely of nucleated forms, appearing in the circulation in man (Morris,[89] Hirschfeld and Weinert,[74] Muehlbradt[90] and many others) which sometimes persist over long periods. Similar findings have been reported in animals (mice, Lauda and Haam;[91] rats, Waltz;[92] rabbits, Karlbaum,[93] Ponticaccia;[78] guinea pigs, Keller;[31] dogs, Loesch, Witts and Zimmermann,[35] Karlbaum,[93] Takagi,[57] Weicksel and Gebhardt,[63] etc.). This we have never been able to substantiate, even during the period of anemia, though we have returned to the search on numerous occasions and repeatedly on the stained spreads taken at appropriate times. Beyond the occasional normoblast found even in normal dogs' blood, we have not been able to find any nucleated forms on Jolly bodies at any time after splenectomy. Istomanowa, Wjassinkow and Swjatskaja[28] likewise failed to find any "granular crises." Such discrepancies can only be recorded here in the hope that a satisfactory explanation will eventually be forthcoming.

Reticulocytes. The behavior of the reticulocytes immediately after operation has already been discussed. In our experience with dogs from 10 to 42 days after splenectomy (*i. e.*, coincident with the maximum amount of anemia), the reticulocyte would again rise (0.4 to 1.0 per cent), sometimes to stay increased during the period of observation of more than a year (like the bone marrow hyperplasia that we have elsewhere reported). The monkeys, however, never showed any increase, probably on account of the mildness of the anemia. Mole[41] in rabbits and Benhamou and Nouchy[94] only found a transient postoperative reticulocytosis, like that found in the majority of our dogs (as previously noted). We would again emphasize that while reticulocytosis undoubtedly indicates an alteration in erythropoiesis, and possibly a sign of increased erythro-

poietic activity, it is not necessarily and always a sign of such a change. As Witts[95] points out in his recent Goulstonian lectures, "Estimations of the number of reticulocytes have added much to our knowledge of the rate of blood formation in disease, but this test must not be used uncritically, and it needs collateral support. Reticulocytes appear in the blood stream when the marrow is irritated by a variety of substances, such as shellac and colchicin, and marrow irritation must be distinguished from a real increase of red cell production. I have seen reticulocyte counts of 6 per cent in aplastic anemia, though the absolute number was small, and this is not surprising when we remember that a few remnants of hyperplastic marrow are usually left in this disease. An increased delivery of red cells into the circulation may be unaccompanied by a rise in the number of reticulocytes, as when a transfusion is given at the beginning of liver treatment in pernicious anemia." We have already referred to the possibility of a disturbance of normal maturation being the responsible factor.

The Nature of the Anemia. In explanation of the nature of the postsplenectomy anemia, its occurrence is obviously due to the loss of something contained in the spleen. Asher and his school have reported an increased loss of iron after splenectomy, which would afford a satisfactory solution as the anemia is apparently one of decreased blood formation. Not only have their published protocols seemed inadequate to clinch the point, however, but they have not been sufficiently confirmed by others. Our earlier studies on this point having been inconclusive ("The Spleen and Anemia," p. 112 *et seq.*), we have recently returned to this problem with better methods, more animals and varied controls; though the results were not as striking as one might wish, we believe that they confirm Asher's view that there is an increased loss of iron after splenectomy (unpublished studies). We have not been able to prevent the anemia by high iron diets. The situation remains then, as previously stated, that in the light of the evidence at hand, including the stimulating action of splenic extracts (Danilewski,[96] Leake,[97] ourselves and others), the loss of the spleen is thought to produce anemia, not by the loss of a center of blood formation (though this may contribute in some cases) but by the loss of a stimulant to the bone marrow or of one of its purveyors of building material, especially iron. As Lauda[9] points out, analogous to the action of lowered body temperatures in stimulating the heat-producing centers in the medulla, and to the stimulation of respiration by accumulated CO_2 in the blood, so products of erythrocytes destroyed in the spleen may perhaps stimulate blood-cell formation, which stimulus would temporarily be diminished in the absence of the spleen until the process was fully taken over by other members of the reticuloendothelial system. Such increased postsplenectomy activity in liver, lymph nodes and bone marrow has been repeatedly demonstrated (See "The Spleen

and Anemia," pp. 164, 201) and is, I believe, generally accepted. With such a dual action of the spleen in opposing directions (lowering the erythrocyte count by doing away with cells and helping to raise it by stimulating erythropoiesis), it is easier to comprehend the varying results that have so long complicated this problem. Such an explanation, too, is in accord with our findings (since confirmed by others) that the anemia that follows a hemolytic agent, while producing a smaller drop in the splenectomized dog, requires a longer period of repair. It does not produce as great a drop because if anemic, there is less distance to go, also because the cells are more resistant, and one of the agents for removing erythrocytes is absent; but it lasts longer because a stimulant to the bone marrow is absent.

The anemia once established, the increased resistance of the erythrocytes may be regarded as the usual sequel of anemia, while its eventual disappearance is adequately explained by the compensatory bone marrow hyperplasia. The persistence of this hyperplasia may be due, as Johnstone[30] states, to the general law of regeneration in excess; but an added factor for consideration is the cellular increase brought about by the assumption of the absent spleen's hemolytic function.

The Effect of Splenectomy on the Blood Platelet Count.—Kaznelson's[98] demonstration in 1916 that splenectomy had a remarkably beneficial effect on those cases of purpura that had been shown by Frank[99] (1915) to have a low blood platelet count has stimulated considerable interest in this phase of the spleen problem. The rise in the platelet count has been found by all observers both experimentally and clinically, though the evidence varies as to the duration and cause of the increase. Experimentally, for instance, it has been found in dogs by Weicksel and Gebhardt,[63] Binet and Kaplan,[100] Loesch, *et al.*,[35] Steiner and Gunn,[101] and clinically, by Bachman and Hultgren,[71] Benhamou and Nouchy,[94] Dawbarn, *et al.*,[102] Galloway,[103] Holloway and Blackford,[104] Leotta,[105] Litchfield,[106] Quenu and Stoianovitch,[107] Rivoire,[108] and many others. (See also 30 cases reviewed by Leschke and Wittkower,[109] and 101 cases by Spence[110].)

The findings as to the duration of the rise have not been so uniform. In our dogs, the count was from 50 to 200 per cent higher at the end of observation (3 to 12 months) than before operation. Immediately following the operation there was a considerable rise (like that of the "operated" controls) but after a drop toward normal a second rise was observed which was lasting. While others have found this lasting rise (Liles,[111] experimentally, Galloway[103] and in a number of the reports collected by Leschke and Wittkower,[109] and Spence[110]) many others, including 3 of Kaznelson's[98] original cases, have returned to normal (in the experimental observations) or to pathologically low limits (in the cases of thrombopenic purpura), sometimes with and sometimes without return of hemorrhagic symptoms. Such variations have led Steiner and Gunn,[101] on the basis of control operations to splenectomy on rabbits, to conclude

that the thrombocytosis of the latter operation does not differ from the others in time of occurrence, degree or duration. They did not, however, in my opinion follow their test animals for a sufficiently long period to invalid to the majority view that the postsplenectomy thrombocytosis is of considerably longer duration and degree than simple postoperative thrombocytosis. The same increased fluctuation of successive counts ("irritability of the blood picture") after splenectomy has been noted for the blood platelets as for the erythrocyte and hemoglobin determinations (Loesch, Witts and Zimmermann,[35] Sorge,[54] our own observations, and others).

As to the cause of the changes in the platelet count after splenectomy in disease, Frank[99] based the thrombopenia on a deficient formation in the bone marrow, which was then stimulated by removal of the spleen, while Kaznelson[98] believed there was an increased destruction of the platelets in the spleen. Counts of the platelets in the blood entering and leaving the spleen have not decided the matter, though on the whole this evidence favors the thrombolytic action of the spleen, as does the histologic evidence of hyperplasia of phagocytic cells in the spleen in the purpura cases and the suddenness of the rise of the platelet count after splenectomy. The long duration of the experimental thrombocytosis, on the other hand, points either toward the lasting loss of an inhibiting action on platelet formation in the bone marrow or to inadequacy on the part of other members of the reticuloendothelial system to take over the lytic function for platelets; as the system is able to do for erythrocytes. Until decisive evidence is available, it would be reasonable to assume that the postsplenectomy thrombocytosis may be the result of both decreased thrombolysis and decreased inhibition of platelet formation.

Summary. While definite conclusions are obviously impossible on many of these matters, the following statements can be said to have the support of the more weighty evidence.

In the normal mammal, splenectomy causes a true, mild temporary anemia that varies both in individuals and in species and in time of appearance, degree and duration. This is accompanied by an increase in the reticulocyte count, an increase in the resistance of the erythrocytes, both of which are apparently responses to the anemia. This anemia is due to a loss with the spleen of a property which aids erythrocyte formation, such as the conservation of the iron of brokendown erythrocytes. This function is eventually taken over, at least in large part, by other members of the reticuloendothelial system. The normal spleen does not have an inhibitory action on erythropoiesis in the bone marrow.

The reason for the appearance of Jolly bodies and nucleated forms which has been reported by the majority of investigators, has not been explained. It is possible that they represent a loss with the spleen of a property of maturing erythrocytes, rather than the loss of a brake on erythrocytopoiesis.

The cellular hyperplasia in the bone marrow observed after splenectomy represents not only the compensatory response to the anemia but also the loss of an important organ concerned with hemolysis, *i.e.*, many of these hyperplastic cells are functioning on the hemolytic side of the hemolytopoietic system.

Splenectomy both in normal animals and in cases of thrombopenic purpura causes a marked rise in the platelet count, which is more persistent than other postoperative thrombocytoses. It has not yet been settled whether this is due to the removal of a platelet death-house or of an organ that tends to inhibit platelet formation or to both.

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THE VAN DEN BERGH REACTION AND THE BROMSULPHALEIN TEST IN THE ESTIMATION OF HEPATIC FUNCTIONAL IMPAIRMENT.

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Numerous reports in recent years, embodying the results of extensive experience with the use of various methods for the determination of hepatic functional efficiency, almost invariably emphasize the fact that the excretory function of the liver is the only one which can be investigated clinically with any degree of success. This is most unfortunate for, from a practical standpoint, the several metabolic functions of the liver are of much more significance than is its excretory function. Fortunately for the individual with hepatic disease, however, the enormous functional reserve and remarkable regenerative capacity of that organ enable it adequately to maintain its important metabolic activities even in the presence of advanced anatomical changes, particularly if the disease process is chronic in nature. For these reasons attention has been directed particularly toward the diagnostic significance of the van den Bergh reaction, the degree of bilirubinemia and the ability of the liver to eliminate halogenated phenolphthaleins from the blood stream. Bromsulphalein has proved to be the most satisfactory of the latter substances and has been employed extensively in recent years.

The present report constitutes an analysis of the positive findings

obtained by one or more of these methods in 224 determinations made upon 188 patients.

Van den Bergh Reaction. On the basis of differences in color reaction observed when icteric sera are treated with Ehrlich's diazo reagent (diazobenzosulphochlorid), van den Bergh[1] postulated the existence of two types or forms of combination of bilirubin in the blood of jaundiced individuals; one form, present characteristically in obstructive jaundice, was believed to give the so-called immediate direct reaction, forming acetophenolazorubin promptly upon the direct addition of the diazo reagent; the other form responded only after the precipitation of the serum or plasma proteins by alcohol, this type of reaction being supposedly characteristic of hemolytic jaundice. This view was supported by McNee,[2] who utilized this hypothesis as the basis for his conception of the liver lobule as a functional unit in the metabolism of bilirubin whereby the mechanism of production of obstructive hepatic jaundice, nonobstructive hepatic jaundice and hemolytic jaundice could be conveniently explained.

Clinical trial, however, did not appear to justify the belief that various types of jaundice could be accurately differentiated by this method. Varying responses obtained at different times in the same individual have tended to discredit the differential diagnostic value of the van den Bergh reaction. At present many are of the opinion that the type of response is determined solely by the concentration of bilirubin if certain factors such as temperature and hydrogen-ion concentration are controlled. Snider and Reinhold[3] found that as increasing amounts of bilirubin were added to serum the direct van den Bergh reaction changed from negative to delayed, then to biphasic and immediate and, conversely, that dilution of icteric serum with normal serum changed the reaction from immediate to delayed. They conclude that the type of direct van den Bergh reaction observed in serum depends upon the concentration of bilirubin and is independent of the underlying cause of the existing hyperbilirubinemia. The degree of bilirubinemia (icterus index) associated with each type of van den Bergh reaction observed in the present series of patients is shown in Table 1. The van den Bergh reaction was performed according to the method suggested by Lepehne[4] and the icterus index by the method of Bernheim.[5]

Hyperbilirubinemia (icterus index above 6) was present in all but 1 case (I. I. 3.9), its absence in this instance, in spite of obvious hepatic disease (confirmed at autopsy), being presumably due to the existence of a profound secondary anemia. The icterus index range in each group was as follows: positive indirect (negative direct) reaction, 3.9 to 21.8; delayed direct reaction, 12 to 48.8; biphasic direct reaction, 10 to 99; immediate direct reaction, 13.2 to 173.

TABLE 1.—BILIRUBINEMIA IN VAN DEN BERGH REACTION GROUPS.

Icterus index.	Cases.	Direct van den Bergh.			
		Negative.	Delayed.	Biphasic.	Immediate.
3.9	1	1			
6.1–10	44	42	..	2	
10.1–20	103	47	35	20	1
20.1–30	21	1	5	12	3
30.1–40	13	..	3	8	2
40.1–50	7	..	1	6	
50.1–60	12	..	..	6	6
60.1–70	3	..	..	3	
70.1–80	8	..	..	3	5
80.1–90	3	..	..	2	1
90.1–100	1	..	..	1	
100.1–120	2	..	..	..	2
120.1–140	4	..	..	..	4
140.1–180	2	..	..	..	2
Total	224	91	44	63	26

It is evident that considerable overlapping occurs in the different reaction groups. Grouping the negative direct and delayed direct reactions together, since they possess the same clinical significance, all of the cases of hyperbilirubinemia presenting these reactions exhibited icterus index values ranging from 6.1 to 50 (100 per cent). Of the 63 sera giving the biphasic direct reaction 48 (76.1 per cent) fall within the same icterus index range (6.1 to 50). Of the 26 sera giving the immediate direct reaction, 6 (23 per cent) fall within this range. If care is exercised in the performance of the test and in timing the color reactions there is certainly a sufficiently marked difference, particularly between the negative or delayed reactions and the biphasic or immediate reactions, to preclude the probability, suggested by Snider and Reinhold,[3] that this overlapping may be satisfactorily explained on the basis of experimental error. Variations in temperature and hydrogen-ion concentration, although of theoretical significance, are of little practical importance under standard laboratory conditions.

These observations suggest that factors other than the concentration of bilirubin in the serum are involved in the determination of the type of van den Bergh reaction produced. This belief is further supported by an analysis of varying reactions occurring at different times in the same individual (Table 2).

There can be no question but that the transition from the stage of the indirect (negative direct) reaction through the stages of delayed, biphasic and immediate direct reactions is usually associated with a distinct tendency toward an increase in the degree of bilirubinemia. However, exceptions to this general rule were noted in 5 of the 19 cases in this group. In cases J. H., A. C., M. S. and C. M., a biphasic reaction occurred at an icterus index level lower than that associated, at another time, with a delayed reaction.

In case K. R. an immediate direct reaction was obtained at a lower bilirubin concentration than was present with a biphasic reaction.

TABLE 2.—VARIATION IN VAN DEN BERGH REACTION IN SAME INDIVIDUAL AT DIFFERENT TIMES.

		Direct van den Bergh.											
		Negative.			Delayed.			Biphasic.			Immediate.		
Case.	Condition.	I. I.	Dye.*	Chol.†	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.
A. C.	Comm. duct Stricture	....	..	...	34	35	236	30	40				
J. H.	Carcinoma pancreas	9.1	15	162	37	20	180	24	20	210	60	20	230
K. G.	Comm. duct Adhesions	....	..	...	13	..	154						
K. R.	Comm. duct Stone	....	..	...	....	..	...	75	..	...	54.9	50	
J. C.	Comm. duct Stone	7.6	0	...	....	..	...	14.8	40				
A. S.	Comm. duct Stone	10.9 11.2	0	...	....	..	...	37					
C. P.	Pernicious anemia	9.0	..	88	13.3	..	92						
R. G.	Icterus Neonatorum	.... 8.4	..	...	48.8 18 15	..	104						
M. S.	Myocardial insufficiency	....	.. ..	... ...	20	15 ..	138 ...	17 21.4					
W. W.	Myocardial insufficiency	12	30	...	13.7	35			25				
S. G.	Cholecystitis acute	9.2	10	188	....	..	...	....	...	...	59	80	240
C. D.	Cholecystitis	9.2	0	...	17.7	0	300						
H. H.	Cholecystitis	11.6	15	...	12	15							
J. K.	Cholecystitis	11.6	3	...	12.1	5	164						
A. D.	Cholecystitis Cholelithiasis	10 12 13 13	.. 20 8 5	136 142	....	.. ..	... ...	63 42 33 33	.. 80 80 50	150 184	129	80	136
S. S.	Cholelithiasis	13.6	30	...	....	..	...	60	100	144			
F. C.	Cholelithiasis	9.9	0	...	....	..	...	26	30	141			
C. M.	Cholelithiasis	....	..	...	24 33	.. 25	227	16	30				

* Dye retention in percentage. † Cholesterol in milligrams per 100 cc.

Such discrepancies, particularly in the delayed and biphasic reactions, cannot be disregarded when attempting to evaluate the significance of the van den Bergh reaction. Results of dilution experiments such as those reported by Snider and Reinhold[3] permit but limited deductions, as the concentration of variable factors, other than bilirubin, which might influence the response was not controlled. Other things being equal, it is well established that the diazo reaction varies in a definite manner with alteration in the bilirubin content of the serum. Barron[6] found that when sodium bilirubinate, in buffered alkalin solution and giving an immediate direct reaction, is added to normal serum in amounts up to 12 mg. per 100 cc. an indirect (negative direct) reaction is obtained; with increasing concentrations up to 16 mg. per cent, biphasic, and above 16 mg. per cent, immediate direct reactions are produced. Barron concluded, as have others, that immediate coupling of the smaller amounts of bilirubin with the diazonium salt is prevented by the

adsorption of the pigment by some constituent of the serum, probably serum globulin. It was also noted that the preliminary or simultaneous addition of certain surface active substances, which prevent this adsorption of bilirubin, results in the production of an immediate reaction even in the presence of small quantities of bilirubin. From a clinical standpoint the most important of these surface active substances are the bile acids and cholesterol. Qualitative variations in the van den Bergh reaction may therefore presumably be dependent upon variations in the concentration of these factors as well as in that of bilirubin.

TABLE 3.—DEGREE OF BILIRUBINEMIA, BROMSULPHALEIN RETENTION AND CHOLESTEREMIA IN CONDITIONS OTHER THAN GALL-BLADDER DISEASE.

Case.	Condition.	Direct van den Bergh.											
		Negative.			Delayed.			Biphasic.			Immediate.		
		I. I.	Dye.*	Chol.†	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.
J. F.	Catarrhal jaundice	....	..	...	....	..	...	....	..	...	13.2	90	194
J. W.	Portal cirrhosis	10	20	165									
R. C.	Portal cirrhosis	....	..	...	....	..	...	18.1	70	162			
L. S.	Arsenical hepatitis	....	..	...	....	..	...	54	35	96			
J. V.	Arsenical hepatitis	....	..	...	....	..	...	....	..	...	102	90	110
											60	90	
											56	75	
C. Z.	Acute yellow atrophy	....	..	...	....	..	...	....	..	...	129	100	84
R. S.	Acute hepatitis	....	..	...	....	..	...	....	..	...	75	80	182
M. M.	Acute hepatitis	10.1	0	...	25.9	80	176						
					17	25							
J. M.	Acute hepatitis	....	..	...	....	..	...	18.8	60	...	80	95	148
G. T.	Acute hepatitis	....	..	...	....	..	...	60	50	180			
S. L.	Acute hepatitis	....	..	...	....	..	...	43	40	142			
F. L.	Myocardial failure	....	..	...	15.5	5							
E. Y.	Myocardial failure	....	..	...	16	0	176						
W. W.	Myocardial failure	12	30	166	13.7	30							
M. S.	Myocardial failure	....	..	...	20	5	138	17	15				
A. S.	Myocardial failure	11.2	5	376									
W. M.	Myocardial failure	....	..	...	....	..	...	15	0				
J. G.	Myocardial failure	....	..	...	....	..	...	....	..	...	26	30	
H. L.	Banti's disease	....	..	...	....	..	...	15.0	0				
O. P.	Banti's disease	12.8	0	105									
J. C.	Banti's disease	....	..	...	....	..	...	33	20				
I. C.	Banti's disease	11.1	10										
S. T.	Pernicious anemia	....	..	...	16	0	100						
C. P.	Pernicious anemia	9	0	104	13.3	0	96						
A. P.	Pernicious anemia	....	..	...	14.1	0							
A. H.	Pernicious anemia	....	..	...	14.4	0							
J. H.	Hemolytic jaundice	....	..	...	12	0	110						
C. G.	Icterus neonatorum	12	0										
K. G.	Icterus neonatorum	8.4	0	...	18	0							
J. K.	Acute leukemia	....	..	...	13.8								

* Dye retention in percentage. † Cholesterol in milligrams per 100 cc.

In this series there is no apparent correlation between the plasma cholesterol content and the type of van den Bergh reaction (Tables 2, 7 and 8). Examination of the data reported by Meyer[7] in a study of liver function in diabetes mellitus likewise reveals no such correlation. Unfortunately, no satisfactory method is yet available

for the quantitative determination of bile acids in blood, so that the influence of that factor in clinical conditions cannot be accurately investigated. Analysis of the data presented in Table 2, however, appears to indicate that the state of hepatic function, as evidenced by the degree of retention of bromsulphalein, may play an important part in determining the type of reaction. It may be noted that in those instances in which a biphasic reaction was produced at a lower level of bilirubinemia than a delayed reaction the degree of bromsulphalein retention was invariably greater at the time the former response was obtained. Although the underlying cause of the change in reaction remains in doubt, these observations support the view originally held with regard to the clinical significance of the biphasic direct reaction as being indicative of hepatic functional impairment. In Table 3 are presented the findings in cases of hepatic cirrhosis, acute toxic necrosis of the liver, hepatitis, myocardial failure, pernicious anemia, Banti's disease and hemolytic icterus. It is of interest to note that in one patient with catarrhal jaundice an immediate direct reaction was obtained with an icterus index of 13.2.

TABLE 4.—CARCINOMA OF PANCREAS.

Case.	Direct van den Bergh.											
	Negative.			Delayed.			Biphasic.			Immediate.		
	I. I.	Dye.*	Chol.†	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.
J. H.	9.1	15	162	37	20	180	24	20	210	60	20	230
A. C.	...	..	...	..	..	...	30	10	210	74	25	236
							30	15	214			
L. G.	...	..	...	..	..	...	66	40	234			
H. G.	...	..	...	..	..	...	84	30	192			
							99	30	202			
C. B.	...	..	...	..	..	...	..	..	...	76	30	
H. C.	...	..	...	..	..	...	..	..	...	108	60	348
H. D.	...	..	...	..	..	...	..	..	...	173	90	224
M. W.	...	..	...	..	..	...	..	..	...	85.7	35	246
										34.5	20	197
E. F.	...	..	...	..	..	...	..	..	...	30	30	184

* Dye retention in percentage. † Cholesterol in milligrams per 100 cc.

The conclusion seems justifiable that repeated determinations of the van den Bergh reaction and the observation of its transition from one type to another in individuals with biliary tract disease are of considerable significance if interpreted in conjunction with estimations of the degree of bilirubinemia and bromsulphalein retention. As stated by Barron,[6] although the diazo reaction behaves in severe nonobstructive jaundice just as in obstructive jaundice, it differs in that in the former case the transition from a negative or delayed direct reaction is relatively slow, occurring only

in consequence of hepatic polygonal cell destruction, whereas in the latter the change takes place rapidly, frequently within a few hours after complete obstruction has occurred. The qualitative phase of the van den Bergh reaction is deserving of more clinical study than has recently been devoted to it.

Bromsulphalein Retention. The bromsulphalein dosage employed was 2 mg. per Kg. of body weight, with which quantity no 30 minute retention has been observed in large numbers of control studies in individuals without biliary tract disease.

In many of the reported studies of the bromsulphalein test the statement is made that, except in portal cirrhosis, retention of the dye occurs only in the presence of hyperbilirubinemia, the degree of retention of dye and pigment being approximately parallel. This conclusion was reached by Piersol and Rothman[8] and by Foley.[9] The data presented by the latter, however, also indicate a disproportionately high degree of dye retention in patients with myocardial failure and passive congestion of the liver. The present series contains an unusually large number of cases in which the degree of bromsulphalein retention was out of all proportion to the bilirubin concentration of the blood serum. The majority of these findings were in patients with cholecystitis with and without cholelithiasis. The most striking examples of these observations are presented in Table 5. It may be noted that in 3 cases 100 per cent retention of the dye occurred in individuals with icterus index values of 8.3, 7.2 and 8.7, respectively (cases B. A., E. T. and W. V.). The presence of hepatic functional insufficiency in these 3 cases was further evidenced by the high concentration of urobilinogen in the urine (1 to 150, 1 to 100 and 1 to 200 respectively). Physical examination revealed no evidence of hepatic enlargement, the diagnosis being subsequently confirmed at operation. The question of bromsulphalein retention in gall-bladder disease will be considered below. It is obvious, however, from these data, that the bromsulphalein test may be of great practical value in determining the operative risk and the most suitable time for operative intervention in surgical disorders of the biliary tract associated with but mild hyperbilirubinemia. Cases such as those represented in Table 5 are unquestionably complicated by impairment of hepatic functional efficiency which, if unrecognized, may lead to serious postoperative consequences. Under such circumstances the glycogenic function of the liver is usually impaired, as indicated in a study of ether hyperglycemia reported by Gehret and the author,[10] although the methods available clinically for the estimation of this important function usually fail to disclose evidence of serious disturbance (glucose, levulose and galactose tolerance tests).

In Table 6 are presented data which further illustrate the lack of correlation between icterus index values and the degree of bromsulphalein retention in certain cases. Repeated observations in the

same case may reveal independent variations in these two factors, indicating an apparent dissociation of two phases of a single function, excretion; *i. e.*, the ability of the liver to excrete bilirubin, a normal excretory product, may vary independently of its capacity for eliminating bromsulphalein, a foreign substance.

TABLE 5.—BROMSULPHALEIN RETENTION WITH LITTLE OR NO HYPERBILIRUBINEMIA.

Case.	Condition.	Direct v. d. B.	I. I.	Dye.*	Chol.†	Urobilinogen.
M. D.	Cholecystitis (stone)	Negative	9.8	35	146	1–60
A. D.	Cholecystitis (stone)	Negative	10.0	20	150	
M. R.	Cholecystitis (stone)	Negative	7.8	50	198	1–40
		Negative	6.2	20		
		Negative	8.1	20	347	
		Negative	7.4	20		
M. S.	Cholecystitis (stone)	Negative	8	20	...	1–30
B. A.	Cholecystitis (stone)	Negative	8.3	100	162	1–150
E. S.	Cholecystitis (stone)	Negative	8.4	10	165	
		Negative	8.6	10		
S. G.	Cholecystitis (acute)	Negative	9.2	10	188	
E. T.	Cholecystitis (chronic)	Negative	7.2	100	210	1–100
		Negative	7	5	...	1–40
W. V.	Cholecystitis (chronic)	Negative	8.7	100	226	1–200
N. H.	Cholecystitis (chronic)	Negative	7.4	10	156	1–350
J. M.	Cholecystitis (chronic)	Negative	6.7	30	...	1-80
V. R.	Cholecystitis (chronic)	Negative	9.6	10		
H. H.	Cholecystitis (chronic)	Negative	7	10	...	1–40
P. M.	Cholecystitis (chronic)	Negative	8.9	20	180	
		Negative	9.9	15	184	
A. D.	Cholecystitis (chronic)	Negative	8	10		
J. W.	Portal cirrhosis	Negative	10	10		
W. M.	Myocardial failure	Negative	9.2	10		
L. R.	Alcoholism	Negative	8	15		
M. G.	Duodenitis	Negative	8.8	20		
S. S.	Duodenitis	Negative	9.7	10	202	
G. J.	Adrenal neoplasm	Negative	3.9	10		

* Dye retention in percentage. † Cholesterol in milligrams per 100 cc.

TABLE 6.—INDEPENDENT VARIATION OF BROMSULPHALEIN RETENTION AND BILIRUBINEMIA.

Case.	Condition.	I. I.	Dye.*	I. I.	Dye.	I. I.	Dye.	I. I.	Dye.
A. D.	Cholecystitis (stone)	10	0	12	20	13	8	13	5
		42	80	33	80	33	50		
M. R.	Cholecystitis (stone)	7.8	50	6.2	20	8.1	20	7.4	20
E. T.	Cholecystitis (chronic)	7.2	100	7.0	5				
P. M.	Cholecystitis (chronic)	12	5	8.9	20	9.9	15		
H. V.	Arsenical hepatitis	102	90	60	90	56	75		

* Dye retention in percentage.

Cholecystitis and Cholelithiasis. In this series of 188 patients presenting either hyperbilirubinemia or bromsulphalein retention or both, there were 70 individuals with gall-bladder disease, 34 of

whom were suffering with chronic cholecystitis, 4 with acute cholecystitis and hepatitis, 26 with cholelithiasis and 6 with chronic cholecystitis complicated in 4 instances by chronic hepatitis, in 1 by obstructive biliary cirrhosis and in 1 by diabetes mellitus. In all cases the diagnosis was made by cholecystography supplemented, in most instances, by biliary drainage. In the majority of cases the diagnosis was subsequently established by operation. In the period of 32 months covered by these observations, similar studies, with negative results, were made upon 164 additional patients with

TABLE 7.—CHRONIC CHOLECYSTITIS.

Case.	Direct van den Bergh.*					
	Negative.			Delayed.		
	I. I.	Dye.†	Chol.	I. I.	Dye.	Chol.
C. C.	20	5	186			
M. D.	11.4	20	194			
E. D.	11.2	10				
E. F.	....	...	...	13.2	10	
J. H.	12	10	...	12	15	160
F. H.	....	...	...	12	0	
N H.	7.4	10	156			
J. K.	11.6	3	...	12.1	5	164
A. R.	13.2	20	184			
E. S.	12	30				
E. B.	8.6	5				
E. T.	7.2	100	210			
	7.0	5				
W. V.	8.7	100	226			
H. L.	....	...	...	18	20	160
P. M.	12	5	180			
	8.9	20				
	9.9	15	184			
F. M.	9.1	5	126			
T. M.	9.4	5				
M. M.	....	...	...	12	0	176
W. P.	12.7	10	180			
H. P.	....	...	...	18.4	0	180
J. S.	12	5	190			
F. M.	9.6	5	160			
M. M.	9.4	5	140			
J. P.	12.4	0	190			
L. J.	12.3	10	154			
G. G.	....	...	...	14.8	20	162
F. C.	12.8	10	180			
D. D.	9.2	0	...	17.7	0	300
C. C.	8.1	5	190			
	10	15	184			
E. Z.	12	10	180			
G. K.	....	...	...	13.2	20	243
J. M.	6.7	30				
V. R.	9.6	10				
H. H.	7	10				

* There were no biphasic or immediate reactions in this group.
† Dye retention expressed in percentage.

gall-bladder disease. In our experience, therefore, approximately 30 per cent of all individuals with gall-bladder disease, whether or not associated with cholelithiasis, manifest either hyperbilirubinemia or bromsulphalein retention or, in most cases, both. The data pertinent to this group are tabulated in Tables 7, 8 and 9.

TABLE 8.—CHOLECYSTITIS AND CHOLELITHIASIS.

Case.	Direct van den Bergh.											
	Negative.			Delayed.			Biphasic.			Immediate.		
	I. I.	Dye.*	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.*	Chol.
G. D.	....	...	...	....	..	...	50	20	210			
M. D.	9.8	35	146									
A. D.	10	20	136	....	..	...	63	80	150	129	80	136
	12	20	...	....	..	...	42	80				
	13	8	...	....	..	...	33	80				
	13	5	142	....	..	...	33	50	184			
A. F.	....	...	...	27.4	0							
C. G.	....	...	...	....	..	...	56.3	50	222			
R. K.	....	...	...	13.1	30	...	16	60	157			
L. K.	....	...	...	....	..	...	32	50	254			
M. R.	7.8	50	198									
	6.2	20										
	8.1	20	347									
	7.4	20										
M. R.	....	...	...	....	..	...	37	20	210			
D. S.	....	...	...	....	..	...	14	15	240			
M. S.	8	20	146									
S. S.	13.6	30	...	....	..	...	60	100	144			
A. W.	11.8	5	147									
B. A.	8.3	100	162									
M. C.	....	....	...	12	0	188						
F. C.	9.9	0	...	....	..	...	26	30	141			
M. D.	10.4	5	168									
E. S.	8.4	10	165									
	8.6	10										
C. M.	....	...	...	24	..	227	16	30				
				33	25							
J. P.	....	...	...	20	40	194						
A. R.	13.2	15	184									
R. W.	11.8	10	147									
M. Z.	7.8	5										
	11.2	35	205									
F. N.	....	...	...	....	..	...	37	15	245			
S. S.	8.7	5	186									
W. D.	....	...	...	....	..	...	....	...	...	40	30	226

* Dye retention expressed in percentage.

In the cases of chronic cholecystitis uncomplicated by cholelithiasis or clinically demonstrable hepatic disease the van den Bergh reaction was either indirect (negative direct) or delayed direct, the degree of bromsulphalein retention varying from 0 to 100 per cent. In the patients with acute cholecystitis and hepatitis,

cholelithiasis, or chronic cholecystitis associated with hepatitis or cirrhosis, reactions of all varieties were observed, varying in some instances in the same individual, as illustrated in Table 2.

TABLE 9.—CHOLECYSTITIS WITH COMPLICATION.

Case.	Complicating condition.	Direct van den Bergh.											
		Negative.			Delayed.			Biphasic.			Immediate.		
		I. I.	Dye.*	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.
H. F.	Chronic hepatitis	....	..	...	13.2	25	104						
L. L.	Chronic hepatitis	....	..	...	....	..	...	12.5	30	200			
M. C.	Acute hepatitis	....	..	...	....	..	...	20.	40	110			
T. D.	Acute hepatitis	....	..	...	....	..	...	46.8	90	94			
M. D.	Acute hepatitis	....	..	...	....	..	...	75	100				
J. M.	Acute hepatitis	....	..	...	....	..	...	18.8	40	...	132		
											80	..	148
A. L.	Chronic hepatitis	10	5										
		10.4	..	192									
S. G.	Chronic hepatitis	9.2	10	188	....	..	...	....	...	...	59	80	240
C. O.	Diabetes	11.5	20	280									
N. M.	Cirrhosis	....	..	...	....	..	...	42	40	120	162	60	164
								56	...	77			

* Dye retention expressed in percentage.

Greene, Snell and Walters[11] noted that in experimentally produced obstructive jaundice, bromsulphalein retention roughly paralleled the degree of bilirubinemia. In the present series this relationship is maintained to a certain extent in clinical obstructive jaundice if such cases are compared with one another (Tables 4 and 8). It is apparent, however, that dye retention may occur in patients with chronic cholecystitis at much lower levels of bilirubinemia than in obstructive jaundice, particularly if due to carcinoma of the pancreas with relatively little hepatic functional disturbance. In individuals with cholelithiasis and common duct obstruction due to stone, superimposed upon the conditions which are common to all cases of obstructive jaundice are those associated with chronic cholecystitis, which may include hepatic functional insufficiency with consequent higher grades of bromsulphalein retention than may occur in pancreatic carcinoma with the same serum bilirubin content.

These findings in gall-bladder disease are not in accord with data reported by most investigators, which appear to indicate that bromsulphalein retention does not occur in cases of chronic cholecystitis without stone or clinically demonstrable hepatic disease. The statement is also frequently made that under such circumstances hyperbilirubinemia is not observed.

In our experience the chief practical significance of the van den Bergh reaction, the bromsulphalein test and the icterus index determination lies in the fact that abnormal findings may and do occur in a considerable proportion of patients with chronic cholecystitis, with or without cholelithiasis, without other clinical evidence of disturbed hepatic function. If the observations of Rosenthal and

White,[12] indicating that the degree of bromsulphalein retention is proportional to the amount of hepatic tissue removed from experimental animals, are applicable to clinical conditions, it would seem that in certain cases of gall-bladder disease with but slight impairment of the bilirubin excretory function, the greatly diminished capacity of the liver for eliminating bromsulphalein is comparable to that which would occur in organic disease involving practically all of the functioning hepatic tissue. The basis for the existing impairment of hepatic function in these individuals is difficult to determine. The disturbance must be widespread, involving a considerable portion of the liver, and nevertheless, must be readily amenable to correction, since essentially normal findings may be obtained within a relatively short space of time following the institution of proper therapeutic procedures. These criteria suggest that the hepatic disorder is largely "functional" in nature, secondary to organic disease of the gall bladder or bile ducts and associated, if with any, with but slight organic disease of the liver parenchyma. Failure to recognize the presence and significance of hepatic dysfunction in such cases is responsible for much of the postoperative morbidity and mortality of biliary tract surgery.

Summary and Conclusions. 1. Analysis of observations on the degree of bilirubinemia, bromsulphalein retention and the van den Bergh reaction in a group of 188 patients showing abnormal response to one or more of these studies appears to indicate that the type of diazo reaction is not determined solely by the serum bilirubin content.

2. The type of van den Bergh reaction appears to bear a more direct relation to the degree of bromsulphalein retention than to the degree of bilirubinemia except in cases of extra-hepatic obstructive jaundice.

3. There is no direct correlation between the type of van den Bergh reaction and the plasma cholesterol concentration.

4. Repeated determinations of the van den Bergh reaction and the observation of its transition from one type to another in individuals with biliary tract disease are of considerable significance, if interpreted in conjunction with the estimation of the degree of bilirubinemia and bromsulphalein retention.

5. Of 234 patients with cholecystitis with and without cholelithiasis, 70 presented either hyperbilirubinemia or bromsulphalein retention or both. Of these, 34 were cases of chronic cholecystitis, without cholelithiasis and with no other demonstrable evidence of hepatic disease.

6. In 3 cases of gall-bladder disease there was 100 per cent retention of bromsulphalein at the end of 30 minutes, associated with icterus index values of 8.3, 7.2 and 8.7. These findings suggest dissociation of these two phases of the excretory function of the liver.

7. This disturbance of hepatic function in patients with gall bladder disease appears to be largely "functional" in nature and associated with but slight demonstrable organic disease of the liver parenchyma.

8. More careful routine preoperative study of patients with surgical disorders of the biliary passages and proper preoperative treatment will perhaps greatly diminish the postoperative morbidity and mortality of biliary tract surgery.

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CLINICAL REACTIONS TO VACCINES AS GUIDES IN TREATMENT.*

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A recent reporter[1] tells of four British pathologists of repute who recommended dosages of autogenous streptococcal vaccines in amounts so variable as are the figures 1 and 27,000. "After this,"

* Read before the Section on Medicine of the New York Academy of Medicine, February 16, 1932.

he comments, "one cannot wonder that many scoff at vaccine treatment." Perhaps the poor repute in which vaccine therapy is held by so many clinicians may be due in part to the fact that its aid has been sought rather indiscriminately. Thus, in Murray's[2] opinion, not much importance should be placed upon the dissatisfaction with vaccines cited by Irons,[3] because it is believed that at the time of his investigation vaccines were being indiscriminately employed, whereas today recourse to this form of therapy is being restricted more properly to suitable patients. Another reason may be that there has been in some cases a lack of thoroughness in observing the minutiæ of the effects of vaccine injections as guides in treatment. Lieb[4] thinks that most of the cases of failure of vaccine therapy are due to improper composition and preparation of the material used or to its faulty administration. He holds that results can be improved by better methods of selecting the bacteria and by better control of the dosage, and he insists that patients should be submitted to a rigid cross examination as to previous reactions before decision is made upon each treatment injection. Hicks[5] recalls the fact that many users of vaccines in the past administered them by rule of thumb at stated intervals and hoped for the best. He is convinced that many of the failures of vaccine therapy are due to lack of appreciation of the extreme variability in the sensitiveness of an individual to his vaccine. Kolmer[6] also upholds these principles and feels that such therapy is worthy of further use when conducted with due regard for important technical details of preparation and administration of vaccines.

It is the desire of the present writers, by describing a method of performing vaccine skin tests and of interpreting their reactions, to help improve the technique of vaccine therapy, especially in the case of patients sensitized to bacterial substances. The essential basis of the presentation is clinical experience; a discussion of theoretical questions is purposely reserved for a later communication.

It appears that vaccine skin tests, when properly conducted, may afford accurate information concerning the reactivity of a human being to bacteria, whether the testing material be made from organisms existing in his body or derived from other sources. In order to obtain and use such information to advantage it is necessary to know for what phenomena to look, to record those reactions that may occur and to apply the knowledge thus obtained to the subsequent conduct of the case. It has come to be thought that no observations made upon laboratory animals or upon test-tube reactions can tell so unerringly as can vaccine reactions, whether or not a particular strain of organism is harmful to a certain individual or whether it should be employed as a vaccine in treating the symptoms that may exist.

Inquiries among clinicians who employ vaccine therapy, however, have revealed the fact that but few of them make use of skin tests

as guides and that, among the few who do so, there exists a striking dissimilarity in the methods of observation and of evaluating the significance of the reactions obtained. The establishment of standards of procedure and of interpretation of vaccine reactions should place them upon a recognized basis similar to that occupied by other biologic tests which employ the human skin in place of the microscope or test-tube. The tuberculin test, the Schick and Dick tests have found their place in modern medicine and so, also, it is believed, should vaccine tests, and especially autogenous vaccine tests.

It is purposed, therefore, to describe some of the reactions which have been observed and to endeavor to evaluate their significance as guides in treatment, in the light of 12 years' work in this field. A little fewer than 900 patients who underwent vaccine skin tests received a total number of more than 13,000 vaccine injections. They were, for the most part, persons suffering with asthma, allergic coryza, allergic dermatoses and infectious arthritis. Out of this clinical material there have been collected the case histories of all the patients with asthma supposed to be bacterial in origin, who have been tested and treated with autogenous vaccines. These case histories, 328 in number, furnish the data upon which this presentation is based. Observations made upon the 888 vaccine-tested patients have also contributed their share to opinions held by the present writers, but all numerical statistics are based solely upon information derived from the records of the smaller group.

The 328 asthmatic subjects are of two classes: (1) Those who failed to react positively to full protein tests, and (2) those who, although shown to be sensitive to external allergenic agents, remained unrelieved of their asthma after avoidance of contact with all known offending allergens. The division of asthmatic patients into the two classes of so-called sensitive and nonsensitive cases has been made in order to separate those reacting positively to external proteins from those whose symptoms are due to infection or to unknown causes. This classification appears to be no longer justified in the light of the present-day recognition of bacterial allergy. The fact should be borne in mind that the manifestations of allergy may differ widely according to the species of animal affected and to the nature of the allergic agent.

Twenty-eight patients among this group of individuals reacted negatively to autogenous vaccine skin tests based upon a complete bacterial survey and therefore did not receive vaccine treatment. Two additional negative vaccine reactors did receive vaccine treatment for the purpose of study and their data are included in the series of 300 vaccine-treated asthmatic patients.

The method of vaccine testing which has been evolved consists of isolating in pure culture and preparing as vaccines[7,21,24,27] all culturable organisms with the exception of spore bearers. The basic

requirement is a thorough bacteriologic examination of materials from all possible foci of infection. Attention is chiefly directed to a study of materials from the nares and accessory sinuses, nasopharynx and tonsils, sputum from the deeper air passages and, if necessary, of the feces. In each case the testing vaccine was a 1 per cent suspension of heat-killed bacterial substance[8] in physiologic saline solution with an added phenol derivative as a preservative. The intradermal injection was made with a tuberculin syringe armed with a fine needle. The amount of suspension used for each test was regularly 0.01 cc. A control test with the diluent was always made. Rarely patients were encountered who reacted positively to the phenol derivative. The testing dose of the vaccine was the equivalent of 80 million bacteria of average streptococcus size. The reactions mentioned throughout this article are those such as may follow any vaccine injection, whether administered for testing or for treatment. All of the tests and, for the past 2 years, the majority of the treatment vaccines have been given by the intradermal route.[6,9,10,11]

The use of the skin as a medium for tests with bacteria or their derivatives was inaugurated by von Pirquet in his experiments with tuberculin in 1907.[12] Gay and Force[13] in 1913 made dermal tests with an extract of typhoid bacilli and found local late reactions in typhoid immunes. I. C. Walker, a pioneer worker in this field, made scratch tests upon asthmatic patients, using stock bacterial extracts in 1916.[14] The early wheal reaction to bacterial proteins was the particular phenomenon to which he attributed significance at that time. In describing the late local reaction which has now come to occupy an important place, he wrote: "There is one other type of reaction which appears to be negative or only slight at the usual half-hour interval for reading the results, but the next day this cut appears not unlike a slight infection, the skin surrounding the cut is hot, very red and slightly elevated. Frequently the cut will contain pus which has always proved to be sterile. This type occurs only very occasionally and possibly it should not be called a positive reaction; a more accurate name for the present would seem to be a 'delayed reaction'."

Experiments with the bacterial scratch tests of Walker were made, but paucity of effects led to the adoption of the intradermal route. The results encouraged an active continuance of this research, which has been continued to the present time.

More recent writers have described reactions to bacteria and their derivatives, notably Price,[15] Swift[16] and his associates, Mackenzie and Hanger,[17] Derick and Fulton[18] and Coburn.[19] They record both early and late skin reactions similar to those described herein.

At the outset of this work the interpretation of vaccine reactions[20,21] was based upon an hypothesis to which experience has given sufficient support to warrant its acceptance, in part, at least.

This hypothesis assumes that those bacteria obtained by culture from a patient and which are the cause of his symptoms, especially if the latter are allergic in character will, when properly made into vaccines and injected into his skin, set up specific and significant reactions.[23] The presence of such reactions was and is taken to signify that the organism causing them should be used in treatment of the case provided that all other existing causes have been removed.

As the cases multiplied in number it became evident not only that vaccines cause skin reactions but that other clinical effects are encountered with more or less frequency. Some of these additional phenomena appear to corroborate the teachings of the skin reactions and may also serve as guides in the subsequent treatment. These other reactions will be described and the attempt will be made to appraise their significance. Certain of them appear to be specific and of useful significance when produced by autogenous vaccines. When heterogenous or stock vaccines are used in making skin tests, any reactions that may follow are considered to be equally specific in character and to show that the patient is sensitized to them. One exception to this statement may exist, perhaps, in the case of the so-called general toxic reaction, to be described below. It is not believed, however, that tests made with stock vaccines are of great diagnostic value under ordinary circumstances, because it is not shown that the organisms concerned are present in the patient's body. No more does a positive reaction to a ragweed pollen test made in December signify that an existing coryza is due to pollen.

Focal surgery, whether of the paranasal sinuses, tonsils or any other sites of infection, has received the first consideration in the treatment of all cases within the present category. The rhinologic or other surgeon has been depended upon to drain all infected foci if possible. No delusion has been harbored to the effect that vaccine treatment can cure a focus of pus pent up in a bony cavity or elsewhere. Indeed, when autogenous vaccines were administered to patients whose homologous foci of infection had not been eradicated or drained, there followed either symptomatic or focal reactions or both—the symptoms under treatment were aggravated. It has therefore become apparent that autogenous vaccine therapy is contraindicated in the face of a closed homologous and causative focus of infection. When it is possible for surgery to remove an infected focus which is the sole seat of the cause of symptoms, relief may be confidently expected to follow, at least for a time. The removal of foci, however, is looked upon as but the beginning and not the end of treatment.

After surgical relief of all infected foci has been accomplished, vaccine treatment appears to be at times the agent needed to supplement measures already taken and often completes or prolongs relief otherwise begun. In borderline cases, perhaps more frequently

encountered than any others, where there exist but slight or no apparent lesions of infection, but where there does exist (as for example, in so-called carriers) a sufficient quantity of allergenic bacterial substance within the patient's body to produce symptoms of sensitization—in the cases of this nature vaccine treatment has appeared to afford more or less permanent relief which would be otherwise unobtainable without continuous resort to palliative drugs.

If it now be assumed that properly conducted[21] vaccine tests have been made upon a patient of the properly selected type, for what reactions shall one look—how shall these reactions be read and recorded and how shall vaccine treatment be guided by them? The subjoined descriptions of reactions and other answers to these questions are based upon data contained in the case histories of 300 asthmatic patients to whom allusion has been made earlier in this article. In observing skin reactions it seems that mere inspection of the site of the inoculation is not enough. Such reaction phenomena as local heat, itching, presence of a palpable though invisible nodule and tenderness are not recognizable by the eye alone, but they are of extremely frequent occurrence and are evidently indications that an important biologic process is taking place. Likewise enlarged, tender lymph nodes, malaise, fever, nausea, the onset or increase of allergic symptoms following and due to vaccine injections—all of these deserve to be recognized and appraised and their meaning applied to the planning of the subsequent treatment of any case in which they may occur.

Early Local (Wheal) Reaction. The early positive reaction at the site of injection of a vaccine is a wheal at least 0.5 cm. larger in diameter than any which may appear at the site of the control injection. It frequently has an irregular outline or even pseudopods and is often surrounded by a zone of erythema (areola). Itching may be present. The wheal reaction is at its height in from 10 to 30 minutes and fades soon thereafter. It was seen in two-thirds of the patients treated and occurred at one-third of all the injection sites in the present series of cases. It is encountered more frequently in asthmatic than in arthritic patients. It persistently occurs on retesting or reinjecting for treatment in spite of prolonged vaccine therapy and even after the symptoms under treatment have been relieved.

Significance of the Early Local (Wheal) Reaction. Occurrence of the early wheal reaction is taken to indicate that the vaccine causing it should be used in the treatment of the case. This reaction is of aid in determining subsequent dosage of the vaccine. Should the reaction be very marked, the treatment dose next following is not increased, other things being equal.

In order to record the wheal reaction the circumference of the wheal and of the areola are outlined upon the skin with pen and ink and numbered. When dry, the picture is transferred by contact

to a sheet of damp white blotting paper and this, when dry, is filed for record. The outline, drawn to a scale, of wheal and areola may be copied upon a graph (Fig. 1).

Name, J. D. Date, March, 9, 1932.
Diagnosis, Asthma.

Intradermal Autogenous Vaccine Tests. By J. N.

No.	Organism and source.	One-half hour.	Skin reactions. Day. 2	3	4		Other reactions.
1	Control		R N	N	N		Asthma was worse during the first two days after the tests were made. (A symptomatic reaction.)
2	Staph. aureus Sputum		A T R N N	A T R N	T R N		
3	Strep. viridans Nares		A A T R N	A A T T R N N	A A T R N N		
4	Bac. alkaligenes Stool		A R N	R	R		

N = Nodule 0.5 cm. in diameter; NN = nodule twice as large.
R = Redness. T = Tenderness.
A = Areola; AA = areola 2 cm. in diameter.

FIG. 1.—A Sample Record of a Vaccine Reaction.

Late Local Skin Reaction. The late positive reaction at the site of inoculation is not unlike the Schick reaction in appearance, but in order to observe it properly its component features are noted by touch as well as by sight and with the assistance of the patient's sensations as described in response to questioning. The sum total of the symptoms are recorded graphically as they appear, change and disappear during the days following the test. Any or all of the following symptoms have been observed at the testing site:

(1) An indurated nodule, slightly or not at all elevated above the surrounding surface of the skin and about 0.5 cm. in diameter or larger, sometimes lasting for several or even for many days. Long endurance of it has come to be looked upon as a favorable prognostic

sign if the vaccine treatment can be thoroughly carried out. (2) Redness of the skin over the nodule. (3) A surrounding zone of erythem (areola) from 1 to 10 or more centimeters in average diameter. (4) Tenderness on pressure, usually at the nodule only, but sometimes extending over the whole of an existing areola. (5) Heat at the injection site or over the whole of the areola, usually beginning in from 6 to 12 hours and lasting for 1 or 2 days. (6) Swelling of the whole areola. (7) Lymphangitis, beginning in from 8 to 12 hours and lasting for a day or two, has been observed in about 2 per cent of the patients who showed late local reactions. (8) Pustule or vesicle in the nodule. This is not due to infection, as repeated culturings have always proved sterile. (9) Pigmentation of the surface of the nodule occurs late and is not often seen. (10) Desquamation of the skin over the site of the disappeared nodule is not common but occurs so late that it has doubtless been overlooked at times. Very rarely a slough has occurred at the site of the inoculation.

The features of the late local reaction may be recorded upon a graph (Fig. 1), in which N denotes a nodule 0.5 cm. in diameter; NN or N2, a nodule twice as large. Redness of the nodule is denoted by the letter R; T indicates tenderness on pressure. The findings of the late local reaction are read and recorded upon at least 2 successive days following the test. A late reaction is considered to be positive when, in addition to any features occurring at the control site, there are present during 2 or 3 days, three or more of the component features named above. Such reactions as vesicles and ecchymoses are considered to be positive even though occurring alone, and to indicate that the organisms causing them should be used in vaccine treatment of the case. In general, a late positive reaction is not what is visible at any one time, but rather, the aggregate of symptoms due to the vaccine injection and observed by the operator and the patient during at least 2 days following the tests.

The late local reaction usually grows less or disappears on retesting during a course of vaccine injections. Its waning after repeated injections is taken to be a signal calling for a corresponding increase in the dosage.

Of the asthmatic patients, 272 gave late local reactions to one or more of the autogenous strains with which they were tested.

Significance of the Late Local (Skin) Reaction. A positive late local reaction is taken to indicate that the autogenous vaccine causing it should be used in the treatment of the case. A very marked late local reaction calls for a smaller amount of vaccine to be given in the next following therapeutic dose than does a slight reaction. During the course of a series of treatment injections each late skin reaction helps the operator to determine the amount and the time of the next vaccine dose.

General Toxic Reaction. This term has been selected to express the rather frequently seen symptom-complex following vaccine injections and characterized by malaise, nausea, drowsiness, feverishness and occasionally swollen and tender lymph nodes. Any or all of these symptoms may occur within from 4 to 12 hours after the administration of the vaccine. This reaction occurs only in conjunction with a positive late local reaction.

Significance of the General Toxic Reaction. It signifies that an overdose of vaccine has been administered. It does not appear to furnish evidence for or against a specific action of the vaccine causing it, but it is of aid in determining subsequent vaccine dosage.

Symptomatic Reaction. This name is applied to the onset or increase of allergic symptoms such as bronchospasm, urticaria, joint pains, etc., following within 48 hours after the administration of vaccine. This reaction occurs only in conjunction with a positive local reaction.

Significance of the Symptomatic Reaction. When symptoms under treatment are made worse by a vaccine injection it is obvious that an overdose has been given, and perhaps that an undrained focus of infection exists. The effect of the vaccine in such a case is clearly specific and experience has proved that if proper treatment can be carried out, benefit may be expected to follow. The symptomatic reaction is of aid in fixing upon subsequent vaccine dosage.

Symptomatic reactions were recorded in 37 of the cases treated. Once elicited, this reaction can be expected to occur again if the dose be large enough. It has been endeavored in such cases to keep the dosage below the amount that will cause a repetition of the symptomatic reaction. The ultimate result of vaccine therapy in the patients in whom this reaction was observed was almost uniformly favorable. The 4 patients who showed symptomatic reactions and yet were not relieved after vaccine treatment were 3 in whom there existed inoperable foci of infection, and 1 who was unwilling to continue with the treatment.

Relief Reaction (Temporary). In 45 of the patients quick relief followed the testing or other injection of vaccines. The relief obtained was either partial or complete and occurred within a few minutes or hours after the vaccine injection and lasted for hours or days or even longer. That this relief reaction was not a mere coincidence was shown by the fact that in several of the patients it was elicited on several occasions. In some of the patients this reaction was seen where a larger dose of the respective vaccine would be regularly followed by a symptomatic reaction (asthmatic attack).

Significance of the (Temporary) Relief Reaction. This reaction appears to indicate that a favorable dose of a specific desensitizing substance has been administered. It is therefore an aid in fixing upon subsequent dosage. This temporary relief reaction should

not be confused with the more gradually developing and usually more permanent good results following a successful course of vaccine treatment. Of the patients who exhibited this reaction all but 4 obtained good results from their vaccine treatment.

Focal Reaction. By this term it is intended to signify a lighting-up of symptoms of infection at the site from which the vaccine organisms were obtained. It appears, if at all, within from 4 to 12 hours after administration of the vaccine. It has been observed in but few—perhaps 6—of the patients, but the records are incomplete with regard to the incidence of this reaction.

Significance of the Focal Reaction. A focal reaction is thought to indicate that the vaccine causing it is specifically related to a focus of infection but is not necessarily connected with the allergic or other symptoms that are under treatment. It may indicate the need for focal surgery at a site hitherto unsuspected.

Symptomatic reactions, relief reactions and focal reactions are welcomed by the physician because they indicate that a specifically active vaccine has been found. Their absence, however, is no indication that favorable results of vaccine treatment will fail to occur. In the series of cases here presented, good results were obtained in 132 patients who showed neither the relief nor the symptomatic reaction.

Recurrent Local Reaction. This phenomenon consists of the reappearance of a faded late skin reaction, days or weeks after its disappearance. It follows in from 6 to 24 hours after the reinjection of a vaccine elsewhere on the patient's body. Its incidence has not been completely recorded as it has not been noted many times. It is probable that more careful observation would have disclosed its presence oftener than was the case.

Significance of the Local Recurrent Reaction. At present this reaction does not appear to afford information that may aid in planning subsequent vaccine treatment.

Negative Reaction. This term means, of course, the absence of local and constitutional effects from the injection of a vaccine. In 30 of the patients selected for vaccine testing no reaction followed autogenous vaccine skin tests and consequently vaccine treatment was withheld except that for the purpose of study vaccine therapy was carried out in 2 patients who showed only negative vaccine reactions. They apparently derived no benefit from their courses of inoculations.

Significance of the Negative Reaction. The absence of all reactions appears to indicate that the organisms used are harmless to their host and that they will be of no benefit in treatment and should not be so used. While the negative reaction to testing vaccine injections is taken to be a contraindication for the use of the respective vaccines in treatment, it is, of course, quite different in the case of negative reactions following treatment injections. Here the organisms used

are those that have previously produced positive reactions. Negative reactions to therapeutic injections of vaccines during the course of properly conducted vaccine treatment are the signal for an increase in the dosage.

In recapitulating the indications applicable to the details of vaccine dosage it may be said that an increase in the amount is called for by a very slight or absent local reaction. A repetition of the last preceding dose is indicated in the cases of: (1) Moderate local late reaction; (2) relief reaction. A decrease in vaccine dosage would follow: (1) A very marked late local reaction; (2) a general toxic reaction; (3) a symptomatic reaction; (4) a focal reaction.

Recording Methods. A graph is presented (Fig. 1) showing a plan for recording vaccine tests and their local results. In the specimen case there recorded an early local (wheal) reaction is seen to have occurred in the case of the test made with Staphylococcus aureus recovered from the patient's sputum. The degree of the early reaction here is shown as an indication that the organism causing it should be prepared as a treatment vaccine and be used in treating this patient. Corroborative reason for so doing is found in the record of the late local reaction where, on the second day there was a large red nodule with tenderness and an areola. These symptoms persisted as late as the fourth day.

The late local reaction to the test with Streptococcus viridans from the patient's nares was also positive, as is shown in the columns for the second, third and fourth days. Here the reaction was actually greater on the fourth day than on the third. Such a late increment, when observed, has usually been a reaction to strains of streptococci.[25] As a rule, however, the positive late local reaction is at its height on the second day following the test.

In accordance with the findings recorded in this graph a treatment vaccine would be ordered to be composed of Staphylococcus aureus and of Streptococcus viridans, each in a concentration of five units (an arbitrary standardization, explained elsewhere[7,21,24,27]) to the cubic centimeter of diluent; that is to say, the equivalent of 400 million organisms of average streptococcus size. The initial dose of this vaccine would be 0.5 cc., given intradermally after the acute symptoms due to the testing injections had disappeared. This decrease in dosage from the amount of material employed in the tests is based upon the fact, noted in the graph (Fig. 1), that there was an increase of asthmatic symptoms (symptomatic reaction) following the tests. The amount of treatment vaccine prescribed for the first dose would be one-fourth of that contained in the testing dose. As was already stated, the dose ordinarily administered as a test amounts to 80 million bacteria of average streptococcus size, so that the first treatment dose here mentioned would contain 20 million bacteria of each of the strains contained in the vaccine and suspended in 0.05 cc. of the diluent. There appears

to be no way in which to determine the amount of vaccine most suitable for administration to any patient except by testing him with it. The greatest variability in the degree of reaction is seen in different patients. Some of them require relatively large doses while others are so extremely sensitive to their autogenous vaccines that minute doses produce violent effects upon them.

The interval between doses of vaccine[13] is regulated in each case by the time of disappearance of the more acute symptoms of reaction due to the preceding injection. It is usually from 4 days to 1 week. The presence of a persistent nodule, if it be no longer tender, even though red, need not cause postponement of the succeeding vaccine dose. The same may be said of desquamation over the site of a former nodule and of a lingering icteric hue about it.

The vaccine unit suspension system of Famulener[24,27] has been found to be a material improvement upon the more complicated and less exact manner of reckoning vaccine dosage by the bacterial count. The bacterial counts given herein are for the convenience of readers who are accustomed to estimate dosage in that way.

The degree of concentration of bacterial vaccines has been observed to affect their potency. A given amount of bacterial substance may produce more pronounced reactions when suspended in a large amount of liquid than if administered to a patient in highly concentrated form. This fact has also been observed by Small.[26] It should be borne in mind when ordering or administering vaccines.

The advantage of using a regular form of chart for recording the results of vaccine testing and treatment cannot be overestimated. Blank forms as used by the writers are shown in Figs. 1 and 2.

Date
Name Diagnosis
Composition and source of vaccines used
Other Treatment and Notes

Day.	Dosage.	Local early reaction.	Local late reaction, N. R. T. A., etc.	General toxic reaction.	Symptomatic reaction.	Relief reaction.	Focal reaction.	Return reaction to	Negative reaction.	Remarks, clinical history, results, etc.

FIG. 2.—Form Used to Record Vaccine Treatment and Effects.

Tables 1 and 2 present in statistical form the results which followed treatment based upon and controlled by vaccine skin and other reactions in 300 patients with bacterial asthma. These results are presented in order to illustrate the advantage of using these reactions as guides in treatment.

TABLE 1.—RESULTS OF TREATMENT OF BACTERIAL ASTHMA IN 300 PATIENTS.

	Patients.	Percentage.
Completely relieved	121	40
Materially but not completely relieved	95	31
Unrelieved or but slightly relieved	84	29
Total	300	100

TABLE 2.—DURATION OF RELIEF IN THE 216 PATIENTS IN WHOM FAVORABLE RESULTS WERE SEEN.*

Time.	Patients.	Percentage.
1 to 3 months	20	9.2
4 to 6 months	54	35.0
7 to 11 months	22	10.1
1 to 3 years	96	44.4
More than 3 years	18	8.3
Unrecorded duration	6	3.0
Total number of patients completely or materially relieved	216	

* The known duration of relief is that reported by patients at their last visit or in response to follow-up letters.

TABLE 3.—VACCINE INJECTIONS.

Vaccine skin tests made*	2286
Treatment vaccine injections	6026
Total vaccine injections	8302

* Including cases in which more than one set of vaccine tests were made.

TABLE 4.—INCIDENCE OF VARIOUS TYPES OF VACCINE REACTIONS (328 ASTHMATICS, SUPPOSEDLY BACTERIAL IN NATURE).

	Patients.
Early local reactors	200
Late local reactors	272
Symptomatic reactors	37
(Temporary) relief reactors	48
Negative reactors	30
Incompletely Recorded.	
Focal reactors	...
Recurrent local reactors	...
General toxic reactors	...

Summary. The present attitude of physicians toward vaccine therapy is presented, and attention is directed to the need of a guide in the selection of vaccines for therapeutic use and in the conduct of vaccine therapy.

The clinical reactions observed in 328 asthmatic patients, tested and treated with autogenous vaccines, were found to be useful as guides in therapy. These reactions, as observed, are described in

detail and are offered as criteria in the selection of proper vaccines for treatment and in determining dosage and the intervals between doses.

Great variability in the degree of reaction to vaccines is seen in different persons. Some of them require relatively large doses, while others are so sensitive to their autogenous vaccines that comparatively minute doses produce violent effects. Properly conducted skin testing offers the best means by which to ascertain suitable vaccine dosage.

Conclusions. The plea is made for the adoption of certain standard procedures in all cases in which the employment of vaccine therapy is contemplated, namely:

1. Careful selection of patients, so as to avoid attempting vaccine therapy in persons unfitted for the method.
2. A complete bacteriologic survey of the patients and the preparation of standardized vaccines from all the organisms recovered, except those that are spore bearers.
3. The performance of skin testing with all vaccines so obtained.
4. Careful observation, recording and interpretation of the reactions that follow such tests.
5. Application of the data thus obtained to the subsequent management of the cases.

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THE MEDICAL IMPORTANCE OF FOCAL INFECTIVE PROSTATITIS.

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It is rapidly becoming realized that arthritis of one form or another is the cause of more human morbidity than almost any other disease entity. If to this are added the many other bodily ills that often are due to those same causes that account for most cases of arthritis, one amasses a group of patients of staggering medical importance and touches what is unquestionably mankind's greatest single economic health burden. The truth of these statements is beyond serious questioning, and, yet, the general medical understanding of the subject leaves much to be desired. And because of this much needless suffering is allowed to take place, suffering that could rather simply be prevented.

Few etiologic concepts stand upon a firmer foundation than does the fact that most of these systemic manifestations are the direct result of the absorption of toxic materials from some focus of infection. The recognition of this and the human benefits accruing therefrom mark one of the most striking and brilliant forward steps in the modern medicine. And, though the advance has been great, there has been a definite lagging in certain directions. Certain focal infective areas have been thrown so much into the spotlight of medical attention that they have tended to obscure other foci that, though commonly secondary to them, have at times a place of equal importance. Particularly is this true in regard to infections of the prostate gland.

It can be said without fear of successful contradiction that in the male the outstanding focal infective triad is *teeth, tonsils* and *prostate gland*. The importance of the first and the second is in the mind

of almost every physician, but often the third is only dimly sensed, more often it is not even thought of or known. So true is this latter statement that in 100 unselected patients presenting all sorts of focal infective manifestations in which this infection was a causal factor the average duration of treatment before any prostatic studies whatever were thought of was astonishingly long (4.5 years). The shortest period of treatment before prostatic study was 1 month and the longest 22 years.

The importance of the search for prostatic infection in such cases is well shown by the fact that at least 72 per cent of all males presenting such symptoms have a definite infection in this gland, and most of them cannot be made permanently symptom-free so long as it persists. It is an easily proved fact that at least 35 per cent of all men beyond the age of 35 years carry such a focus of infection, and the observation that this percentage more than doubles in those with focal infective symptoms would suggest that much could be done in the way of the prevention of these disabling conditions if prostatic studies were made a routine in our health examinations of all adult males.

Much of the general neglect of prostatic studies is to be attributed to two things, *viz.:* (1) A rather widespread lack of knowledge regarding the etiology of such infections; (2) the fact that very little attention has been given to the subject from a focal infective standpoint by urologists themselves.

The outstanding misconception regarding the etiology of prostatic infections is the old and grossly erroneous belief that all such infections are of gonococcal origin. The extent to which this thought has become fixed in the medical mind is amply shown by the frequency with which the internist and general practitioner totally, and without study, rule out such infection merely on the patient's statement that he has never had gonorrhea. Nothing could stand upon a less scientific basis and the falsity of few beliefs is more easily shown. In the herein reported 100 focal infective patients in whom the writer demonstrated definite infection in the prostate gland only 2 had had an attack of gonorrhea within 20 years. Only 7 gave a history of ever having had gonorrhea. It thus can be seen upon what a slender thread the belief has hung.

A close study of the etiologic factors underlying such prostatic infections immediately throws it into the foreground that they rarely are primary infections. Their association with dental and tonsillar infections is outstanding. In this series of cases dental infections showed an incidence of 61 per cent and tonsillar 69 per cent. Not only were these foci present but it is everywhere in evidence that they were in by far the vast majority of cases the primary foci from which the prostate obtained its infection. That this is true is shown by the absence of gonorrhea in their histories and by the repeated observation that the prostatic infection almost never can be permanently cured so long as these other foci persist.

TABULATION OF 100 UNSELECTED CASES OF FOCAL INFECTIVE PROSTATITIS.

Initials.	Age.	Duration of symptoms.		Arthritis.	Ocular lesions.*	Other systemic lesions.†	Infected tonsils.	Infected teeth.	Later tooth infections.	Reactions following massage.
		Yrs.	Mos.							
S. E.	66	2	..	x	—	—	—	—	—	x
F. L. J.	47	15	..	x	—	—	x	—	—	—
R. B. T.	40	8	..	x	—	x	x	x	x	x
S. F.	40	2	..	x	—	—	x	x	x	x
F. W. B.	30	..	6	x	—	—	—	—	—	—
J. S. K.	52	3	..	—	x	x	x	x	—	x
W. T.	42	12	..	—	—	x	x	x	x	x
H. F.	30	10	..	—	—	x	x	—	—	—
P. M.	74	..	6	—	—	x	—	—	—	—
J. C. L.	36	3	..	—	—	x	x	—	—	x
C. K.	57	..	5	—	—	x	—	—	—	—
E. M. J.	49	6	..	—	—	x	x	x	x	—
A. R.	58	7	..	—	—	x	x	—	—	—
A. C.	55	..	1	—	x	—	x	—	—	x
C. D.	49	..	2	—	x	—	—	x	—	x
H. B. C.	45	3	..	—	x	—	x	x	x	x
J. G. C.	39	2	..	—	x	—	x	x	x	x
E. P. R.	53	..	3	—	x	—	x	x	x	x
A. D. Y.	62	..	6	x	—	x	x	x	x	x
R. D.	47	5	..	—	—	x	—	x	—	—
P. J.	68	3	..	x	—	—	x	x	x	x
T. D. W.	46	1	6	x	—	—	x	x	x	x
W. H. L.	73	1	..	—	—	x	—	—	—	—
M. C. L.	50	1	..	x	—	—	—	x	x	—
C. Y. L.	54	3	..	x	—	—	x	x	—	x
F. H.	58	1	3	x	—	—	x	x	x	x
G. B. C.	49	..	4	x	—	—	x	x	x	—
E. D. H.	38	15	..	x	—	—	x	—	—	—
P. S. G.	24	1	..	x	—	—	x	x	x	x
H. R. W.	61	3	..	x	—	—	x	x	x	x
S. W. S.	39	..	2	—	—	x	x	—	—	—
L. G.	25	1	..	—	—	x	—	—	—	—
T. H. C.	58	7	..	x	—	—	—	x	x	—
G. C.	25	4	..	x	x	—	—	—	—	x
G. H. B.	58	2	..	x	—	—	—	—	—	—
C. B.	47	3	..	x	—	—	—	x	—	—
J. H. H.	47	9	..	x	—	—	x	—	—	—
W. E. C.	48	..	9	x	—	—	x	x	x	x
F. J. L.	33	6	..	x	—	—	x	x	x	x
W. W. B.	36	8	..	x	—	—	x	x	x	x
L. M. U.	50	2	..	—	—	x	—	—	—	—
A. Z.	29	5	..	—	—	x	x	—	—	—
C. H. M.	61	2	..	—	—	x	—	—	—	—
W. C. S.	50	3	..	—	—	x	x	—	—	—
H. M. C.	62	15	..	x	—	—	—	x	x	—
O. J. S.	48	1	..	x	—	—	x	x	x	x
W. W.	49	20	..	x	—	—	—	—	—	—
E. L. B.	55	12	..	x	—	—	x	—	—	x
M. C. D.	55	3	..	—	—	x	x	x	—	—
C. E. W.	68	20	..	x	—	—	—	—	—	—
W. H. B.	57	12	..	x	—	—	—	—	—	x
G. B.	58	5	..	x	—	—	x	x	—	x
A. B.	28	1	..	x	—	x	x	—	—	x
E. C. D.	39	10	..	x	—	x	x	—	—	—
L. W.	39	..	9	x	—	—	x	x	x	x
R. P. B.	60	2	9	x	—	—	x	x	x	x
W. A. A.	31	4	..	x	—	—	x	x	—	x
F. C.	51	..	1	x	—	—	x	x	—	—
W. F. B.	54	1	..	x	—	—	x	x	—	x
M. G.	64	6	..	x	—	x	—	x	x	x
A. G.	55	20	..	—	—	x	—	—	—	—
J. H.	42	..	2	x	—	—	—	x	—	x
B. G. H.	64	..	4	x	—	—	x	—	—	—
W. B. W.	52	..	1	—	—	x	x	—	—	x

TABULATION OF 100 UNSELECTED CASES OF FOCAL INFECTIVE PROSTATITIS.
(*Continued.*)

Initials.	Age.	Duration of symptoms.		Arthritis.	Ocular lesions.*	Other systemic lesions.†	Infected tonsils.	Infected teeth.	Later tooth infections.	Reactions following massage.
		Yrs.	Mos.							
W. W. R.	51	1	1	x	—	—	x	x	x	x
R. S.	48	1	..	—	—	x	x	—	—	—
S. T.	62	15	..	x	—	—	x	x	—	x
T. M. T.	56	4	..	x	—	—	x	x	—	x
D. F. V.	70	1	..	—	—	x	—	x	x	x
J. O.	26	..	4	x	—	—	—	x	x	x
J. L. P.	65	5	..	x	—	—	x	x	x	—
J. F. B.	27	11	..	x	—	—	x	—	—	—
R. M. C.	39	10	..	x	—	—	x	—	—	—
W. B. B.	50	..	3	x	—	—	x	x	x	x
E. F. J.	41	4	..	x	—	—	x	x	—	—
H. M. W.	53	2	..	x	—	—	x	—	—	—
W. M. M.	23	4	..	x	—	—	x	—	—	—
C. D.	49	2	..	—	x	—	x	x	x	x
J. G.	39	9	..	—	x	—	x	x	x	x
F. A. C.	53	..	1	—	x	—	x	x	x	x
R. J. B.	37	22	..	x	—	x	x	x	x	—
S. R. B.	46	..	2	—	x	—	x	x	—	—
A. A.	38	1	..	x	—	x	—	—	—	—
W. T. B.	54	1	..	x	—	—	x	—	—	—
G. F. D.	52	3	..	x	—	—	x	x	x	—
G. H. P.	62	..	3	x	—	—	—	x	x	—
R. Y. S.	48	..	8	—	—	x	—	x	—	—
W. C. S.	65	2	..	—	—	x	—	x	—	—
L. N.	48	..	4	x	—	—	x	—	—	—
G. M.	65	1	..	x	—	x	—	x	x	x
J. F.	43	5	..	x	x	—	x	—	—	x
F. S.	45	..	7	x	—	—	x	x	x	x
E. R. K.	41	15	..	x	x	—	x	x	—	—
C. F.	57	6	..	x	—	—	x	x	x	x
M. W. H.	35	3	..	x	—	—	x	—	—	—
G. C. D.	60	6	..	x	—	—	x	x	—	—
S. W. C.	52	7	..	x	x	—	—	x	—	x
F. C.	51	..	1	x	—	—	x	x	—	—
J. R. C.	65	5	..	—	x	—	x	x	—	x
E. P.	50	6	..	—	—	x	—	x	x	x

* Ulcerative keratitis, 6; iritis, 4; uveitis, 2; choroiditis, 2; iridocyclitis, 1.
† Neuritis, 15; muscular, 20; cardiac, 4.

Occasionally prostatic infection may be caused by influenza or some other acute infection. Gastrointestinal and gall-bladder infections occasionally seem to play a part. It is surprising how rarely it has any association whatever with infections in the facial sinuses. The writer has never seen a case wherein he could trace such an etiologic influence and von Lackum[1] has had much the same experience.

Pemberton[2] has ably brought out the thought that there must be an initial systemic factor that probably antedates the determination of all of these infective foci as well as sensitizes the individual to their toxins. Consequently, though the mind is prone to center only on these foci, it has become increasingly obvious that such a narrow view is seldom to the best interest of the patient. In other

words, though all of the foci but the prostatic one may be removed, the patient is rarely a solely urologic problem.

In a review of these patients a number of interesting and important points have presented themselves. Prominent among these has been the great need for a constant watch for other tooth-root infections. Approximately 39 per cent of the patients had such later foci. This is particularly important in view of the fact that it is common custom to attend to existing dental infections and then dismiss the matter from further consideration. Repeated experiences of this sort have caused the writer to lay down the rule that such patients should have a full set of dental Roentgen rays 3 months after the removal of any infected teeth and at 6-month periods for the succeeding 2 years. The number of expensive dental bridges that have had to be removed for some of these later infections would seem to urge the wisdom of delay in this regard in many cases.

One should not dismiss this phase of the subject without a word regarding the tonsils, for some patients cling tenaciously to them. And evidence has not been altogether wanting to suggest that physicians are not always correct when they pronounce tonsils normal. This is further suggested by the fact that a number of those whose speciality has to do with the tonsils have told the writer that often one cannot really tell whether or not a tonsil should be removed until he has it in his hand, which would arouse the suspicion that at times our *dicta* outrun our science.

From a urologic standpoint one can lay down some rather fixed rules regarding the association of the prostatic infection with these more distant foci as well as the patient's systemic symptoms. These might briefly be stated as follows:

1. The prostatic infection cannot be permanently cleared up so long as the causal foci remain.

2. If no improvement is seen in the prostatic secretion after 6 weeks of routine prostatic massage it is probable that there are some other distant foci.

3. If the prostatic infection clears up and then recurs there are other dental infections, providing the tonsils are out.

4. If there are no further dental infections and the prostatic infection recurs the diagnosis of normal tonsils in all probability is wrong.

5. If the distant foci in teeth or tonsils supposedly have been removed and the patient is not markedly improved after 6 weeks of prostatic treatment, one had better investigate the gall bladder or question the last Roentgen ray of the teeth and have it repeated.

6. If these are all negative, and there is no change in symptoms, he can be assured that the prostate has little, if anything, to do with the distant symptoms, and he would do well to center attention on the gastrointestinal tract.

Some years ago the writer called attention to the occurrence of

an increase in the distant symptoms following prostatic massage.[3] In the most severe reactions of this type there was a chill, elevation of temperature and a marked increase in pain, if pain was a symptom of the ailment. In the milder reactions there was but a slight increase in the distant symptoms. The reactions generally occur within 12 hours of the digital manipulation of the gland, last perhaps 12 hours and are followed by a transient improvement beyond that previously existing. The occurrence of this reaction is at times delayed for 24 or 48 hours.

Regarding such reactions one again can lay down some rather fixed rules.

1. Their occurrence is proof that the prostate is a factor in the disease.
2. Their absence does not prove the innocence of the prostatic infection.
3. They occur in at least 50 per cent of the cases.
4. They correspond in every way with a protein or vaccine reaction with a specific affinity for the distant symptom-giving lesion.
5. Being of the nature of a vaccine reaction they urge the wisdom of viewing the prostatic manipulation from the standpoint of vaccine dosage and varying the pressure accordingly.
6. The procedure causing them should not be repeated until at least 3 days after they have subsided.
7. Too profound a reaction reduces the patient's curative response and if prostatic manipulation is too roughly or too often done they may do irreparable harm.
8. They are particularly dangerous in the presence of ocular inflammation.
9. They cause great pain and joint swelling in the presence of marked joint involvement and, if profound, delay cure for many weeks.
10. They rarely occur after more than the first few prostatic massages, but if they continue to follow even the gentlest massage the massage should be discontinued and every effort made to improve the general health before it is started again.
11. Prostatic massage should not be carried out within a week of tonsillectomy or tooth extraction if these have caused any increase of the distant focal infective symptoms.
12. The more acute the distant symptoms for which prostatic massage is carried out the gentler should be the massage. Particularly is this true of inflammations of the eye, wherein subsequent reactions are often severe and prolonged.
13. Except in the most severe cases, the pain of neuritis and arthritis is relieved or banished within four weeks of the institution of regular prostatic massage, providing the prostate is the only infective focus left.

In other places[4,5] the writer has had much to say about the

diagnosis and treatment of prostatic infections, some of which might bear repeating in the present connection. To one who has had much experience with the focal infective prostate it is obvious that these infections differ somewhat from those that result from gonorrhea. In the latter all of the gland follicles become infected so that no normal prostatic secretion is present. Pus is everywhere in evidence in the microscopic field.

In the prostatic infections secondary to more distant foci the infective process often is not so general. In fact, it may be so deeply placed that one may on the first massage obtain only normal secretion, pus being evident only at a later study. So frequently is this the case that it is unwise to pronounce the prostate normal until a normal secretion has been obtained on at least two studies within 3 days of each other. If on the second study there is a quantity of granular débris or an excessive number of lecithin granules a third study should be made.

If digital manipulation of the gland causes any increase whatever in the distant symptoms one can feel assured that, though the obtained secretion be microscopically normal, there is infection present and that further treatment is essential. The occluded follicles soon will begin to drain and pus appear in the secretion. This is not the case with the normal gland. No prostate should be considered normal without microscopic study of its secretion. Palpation is a reliable guide only insofar as it may reveal the presence of tuberculosis, carcinoma or hypertrophy. Hard nodulation of the prostate usually means tuberculosis or carcinoma, for neither of which is massage good treatment.

The hypertrophied prostate is usually infected, and if massage is carried out it should be done with due regard to the possibility of hemorrhage. Pressure should be very carefully made upon the midline, if it is made at all, for such patients often have very thin-walled varicosities in the posterior urethra and at the vesical outlet and dangerous hemorrhage may follow even gentle digital disturbance of the gland.

Prostatic massage in patients known to have tuberculosis of the lung or elsewhere should not be carried out unless it is proved that the prostatic infection is causing distant lesions of such importance as to make it worthwhile to incur the occasional risk of precipitating massive or a miliary tuberculosis. If massage is carried out in such patients it should be continued only to the point of establishing better drainage and not necessarily cure of the local infection.

Massage should not be carried out more often than twice a week and, as has been pointed out, it should be done with the utmost respect for its possible harm. It should be withheld or discontinued just so soon as it does more harm than good. If there are no longer any distant infective foci, and the microscopic appearance of the secretion fails to make further improvement after several

months of treatment, it is advisable to discontinue treatment for 6 to 8 weeks and then start another course of treatments.

If the secretion becomes normal the patient should be restudied several times during the next year to make sure that cure is permanent. A relapse of infection urges the importance of a study for other possible foci in the teeth or elsewhere.[6]

Autogenous vaccines only have served to prolong the infection of those to whom they have been given in this series. This is readily understood when one considers that prostatic massage in these patients forces into the system variable quantities of bacterial toxin, as evidenced by the typical vaccine reaction so often resulting therefrom. This virtual autovaccine therapy must by the nature of things be followed by a negative phase, and one hardly would expect a high degree of immunity effort in an individual in whom every second negative phase was made greater by the administration of a large injection of the same toxin. Particularly should this be true with treatments placed at 3-day intervals.

Summary. 1. The male focal infective triad is teeth, tonsils and prostate gland.

2. Thirty-five per cent of males beyond the age of 35 years have infected prostate glands.

3. At least 72 per cent of males with focal infective symptoms have infected prostates.

4. The focal infective prostate has almost no relation to gonorrhea.

5. Sixty-one per cent of patients with infected prostates have infected teeth and 69 per cent or more have infected tonsils.

6. At least 64 per cent of those having teeth extracted for infection have later infections of other teeth.

7. Roentgen rays should be taken of the teeth in such patients at intervals for at least 2 years.

8. At least 50 per cent of those patients having prostatic infection associated with distant symptoms experience an increase of these symptoms following prostatic massage.

9. These increases in symptoms are analogous to a vaccine reaction and, if too profound, may destroy the patient's curative responses.

10. The pressure of massage must be viewed from the standpoint of vaccine dosage and varied according to the degree of reaction it produces.

11. Great care should be taken in the presence of iritis, ulcerative keratitis, choroiditis and myocarditis not to cause a dangerously severe reaction.

12. It may take several studies of the prostatic secretion in these patients before one is safe in saying the gland is not infected.

13. A distant reaction following massage is proof of infection of the gland and even in the absence of observable pus indicates further treatment.

14. The recurrence of a prostatic infection after cure is almost positive proof of other distant and causal infection.

15. Nodulation of the prostate gland usually means tuberculosis or carcinoma and massage should be withheld until both are proved to be absent.

16. The prostatic secretion should be restudied several times in the year following apparent cure.

17. Autogenous vaccines have proved decidedly disappointing in prostatic infections, seeming to favor chronicity rather than cure.

18. The focal infective picture usually comprises more than attention to the foci of infection alone. Back of it there usually is a patient needing careful medical attention.

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"ASEXUALIZATION" OF THE PLASMODIUM IN INDUCED MALARIA.

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An asexual strain of induced malaria[1] eliminates the possibility of further transmission by mosquitos and precludes the occurrence of malarial relapse after adequate quinin administration. Another practical advantage of such a strain is that screening and isolation of patients becomes a superfluous procedure. Consequently we have attempted to asexualize a sexual strain of benign tertian malaria by continuous human passage. In a previous report[2] of progress dealing with 123 patients it was stated that "after 7 months the sexual strain of malaria began to lose its capacity to produce gametocytes. During the succeeding 9 months this was found to be much more striking in female than in male patients."

At this time additional evidence may be brought forward. Obviously it was impracticable to examine daily smears from all the patients inoculated with malaria in all the New York State Hospitals. However, we did succeed in examining daily smears (Wright-stained) from at least one patient at every passage. Occasionally, when the strain ran out at one hospital, it was necessary to renew it from another. Hudson River State Hospital and the State Hospitals farther south used the so-called "Poughkeepsie strain" exclusively for the purpose of this experiment. The northern State Hospitals continued the "Institute strain" which has been through continuous human passage since 1923 and has always failed during the period of examination to show the presence of any sexual forms (gametocytes).

A word of explanation is relevant as to the microscopic criteria of differentiating sexual from nonsexual parasites in benign tertian malaria. Unless the plasmodium completely fills the red blood cell, it is extremely difficult to make a decision, consequently only fully grown gametocytes have been accurately identified. Further, the chromatin must be localized and not distributed. The question of mosquito infectivity has not been solved, first, because we have not been able to devote sufficient time to breeding mosquitoes in adequate numbers (the few we raised failed to survive) and second, there is always the doubt as to whether enough sexual forms are present to infect a mosquito. In other words, there might be a few sexual forms which failed to infect the mosquito, but such failure would not be a proof of asexuality. Therefore, we have preferred to base our differentiation on careful microscopic examination.

In addition to the 1700 smears from 123 patients previously reported we have since examined 1011 more of the "Poughkeepsie strain," making a total of over 2700, together with over 400 additional slides of the "Institute strain," or more than 3000 smears in all. Smears from 129 patients inoculated with the "Poughkeepsie strain" since August 8, 1929, showed the following distribution up to October 18, 1930; Five females out of 21 patients had gametocytes and 33 male patients out of 90, or roughly about one-third the entire group (omitting those who showed no parasites).

The most striking feature of our data is the fact that after October 18, 1930, *no* patient inoculated with the "Poughkeepsie strain" harbored any gametocytes. Thus the diminution in sexual forms of the parasite as noted in our previous report may be said to have reached its logical conclusion, which is the total absence of gametocytes demonstrable by microscopic methods. Thus the last patient at the Manhattan State Hospital to show gametocytes was inoculated October 17, 1930, and the last patient at Hudson River State Hospital showing gametocytes was inoculated October 2, 1930. This would indicate that the capacity to produce sexual forms died out in this strain at a given age, approximately 2½ years.

In our first report, in 1928, on the "Institute strain" of malaria in use since June, 1923, it was stated that "it is conceivable that gametocytes have been formed at some time in the past, and that the strain has since lost its power to produce sexual forms." The reëxamination of slides from patients inoculated with the "Institute strain" in 1925 failed to reveal the presence of gametocytes. In other words, after about 2 years of continuous human passage no sexual forms were found. The evidence cited above with regard to the asexualization of the "Poughkeepsie strain" would tend to confirm the hypothesis just quoted concerning the "Institute strain." A further examination of 400 smears from patients inoculated with the "Institute strain" failed to reveal any gametocytes.

It is of interest to follow the loss of capacity to produce sexual forms in the "Poughkeepsie strain." The data have been summarized in Table 1.

TABLE 1.—GAMETOCYTES IN BLOOD SLIDES OF MALARIA-TREATED PATIENTS.

	No. of cases.		Average per cent of slides with parasites showing gametocytes.		Actual number of cases showing no gametocytes.		Per cent patients showing no gametocytes.	
	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.
Group 1 (May 9, to Nov. 2, 1928) .	44	14	69	73	0	0	0	0
Group 2 (Nov. 2, 1928 to Aug. 8, 1929)	45	21	16	38	13	1	29	5
Group 3 (Aug. 9, 1929 to Oct. 18, 1930) .	11	55	16	16	6	22	55	40
Group 4 (Oct. 19, 1930 to Mar. 30, 1931)	10	35	0	0	10	35	100	100
Males to May 2, 1931								

In Table 1 it will be seen that in the first 6 months (Group 1) there was a slight decrease in the average percentage of slides with parasites showing gametocytes. In the succeeding 9 months (Group 2) the decrease was more marked, particularly in females. In the 14 months following (Group 3), the percentage had reached the same low level in both males and females (16 per cent). In the last 6 months no gametocytes were found in either males or females.

These results cover a total of 252 patients inoculated with a sexual strain of benign tertian malaria. The loss of capacity to produce sexual forms is clearly brought out in the last column of Table 1, where in both females and males 100 per cent absence of gametocytes is shown. This means that we have been dealing with a true instance of biologic adaptation. Sexual forms are necessary to perpetuate the malarial organism when it has to depend on mos-

quitoes for transmission. But when artificial inoculation replaces the mosquito, sexual forms become superfluous and disappear.

Summary. 1. The continuous human passage of a sexual strain of malaria inoculated into patients with general paralysis on August 8, 1929, has resulted in the complete absence of gametocytes on October 18, 1930. No sexual forms were found after this date.

2. Approximately 2½ years were required to obtain a true biological adaptation of the malarial parasite. Since sexual forms are necessary for the transmission of malaria by mosquitoes, the method of artificial inoculation has rendered them superfluous.

The accumulation of daily smears from consecutive patients has been a difficult and painstaking task. Without the excellent coöperation of the superintendents of the New York State Hospitals and their staffs, the completion of this research would have been impossible. Particular thanks in this respect are due to Dr. C. O. Cheney, Director of the Psychiatric Institute, formerly superintendent of the Hudson River State Hospital, and Dr. I. J. Furman, superintendent of the Manhattan State Hospital.

REFERENCES.

1. Kopeloff, N., and Fiertz, Charles O.: The Clinical Significance of the Life Cycle of the Parasite in Induced Malaria, Am. J. Med. Sci., 1928, **176**, 664.

2. Kopeloff, N.: Inoculation Malaria: Sexual and Asexual Strains, Am. J. Med. Sci., 1930, **179**, 800.

REVIEWS.

TEXTBOOK OF HISTOLOGY. By EUGENE C. PIETTE, M.D. Pp. 466; 277 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, $4.50.

THIS textbook is planned and written along the usual lines of current histologies. As the preface informs us, the figures are taken from various sources. This work will be found useful in certain classes, particularly in dental schools, and while there is nothing strikingly new in the book, it in no way deviates from accepted standards. W. A.

LEHRBUCH DER SPEZIELLEN PATHOLOGISCHEN ANATOMIE, VOL. I. By DR. EDUARD KAUFMANN, Ord. Professor der Allgemeinen Pathologie und Pathologischen Anatomie an der Universität Göttingen, Geheimer Medizinalrat. Pp. 990; 506 illustrations. Leipzig: Walter de Gruyter & Co., 1931. Price, Rm. 55.

EVEN with the monumental system of Henke and Lubarsch, now in its 12th volume, at their disposal, pathologists and advanced students have relied on Kaufmann's textbook of special pathology as a standard for more extended reading than is possible in one volume works. While Reimann's English translation has been a great convenience in this country, it cannot replace the original, so that this new edition after an interval of 9 years is doubly welcome. A scientific book, as well as its readers, is fortunate in being able to pass through 10 editions during the lifetime of its author. Professor Kaufmann, who retired in 1928, has been most industrious in bringing this edition up to date—volume one alone contains over 7500 new references and 68 of the 430 odd illustrations are new and have comprehensive legends. In passing, one regrets that the American literature is not more adequately represented, but presumably it has not been freely available in post-bellum Germany. Among the rewritten topics are angina pectoris, sedimentation rate, blood groups, allergy esophagospasm, eclampsia, endometriosis, as well as larger sections on pulmonary tuberculosis, thyroid and parathyroid, liver and bile passages and so on. Let us hope that the other volumes will soon follow. E. K.

THE COMMONER NERVOUS DISEASES. By FREDERICK J. NATTRASS, M.D. (DUNELM)., F.R.C.P. (LOND)., Assistant Physician, Royal Victoria Infirmary, Newcastle-upon-Tyne. Pp. 218; 15 illustrations. New York: Oxford University Press, 1931. Price, $4.00.

THIS volume is designed for the general practitioner and for it he will be grateful, but it is not sufficiently comprehensive to meet all the needs of the medical student. Such terms as N.A.B., and G.P.I., should be written in full. Epilepsy has been given 18 pages and the psychoneuroses less than half that space—the reverse would be an improvement. General Care of Paraplegic Cases is an excellent chapter. Newer matter that is of practical

use is included such as support by means of adhesive strips in facial paralysis, vaccine treatment of disseminated sclerosis, alcoholic injection of nerve trunks or the Gasserian ganglion in migrainous neuralgia and other worthwhile therapeutic measures.

The author's effort to point out "the possibilities of treatment and to show that these depend generally upon early diagnosis based on appreciation of the significance of symptoms," is achieved. The generous use of cross-reference is helpful, there is a useful bibliography and a good index.

N. Y.

MEDICAL PSYCHOLOGY. Monograph Series No. 54. By WILLIAM A. WHITE, M.D. Pp. 141; 4 illustrations. Washington: Nervous and Mental Disease Publishing Company, 1931.

THE author pleads for the placement of psychology on the same basis as physiology in the medical curriculum. The intention is not for more intensive study of the neuroses and psychoses by the student, "but to orient him with regard to the mental factor as it is seen in disease generally and more particularly in disease of the body, that is, somatic disease." Some such need is great for does not the quack sometimes succeed, with his crude knowledge of psychology, where the regular practitioner has failed? It is unlikely that the medical course shall be lengthened, therefore, if medical psychology shall be accorded serious consideration, a number of other courses must yield a portion of their time, since physiology alone could not afford so much curtailment. The subject-matter is advanced in orderly fashion, with a number of chapters gracefully presented from the psychoanalytic viewpoint.

N. Y.

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE, VOL. 9. TECHNICAL METHODS, GENERAL INDEX. By VARIOUS AUTHORS. Pp. 363; 86 illustrations. London: Medical Research Council, 1931. Obtainable in the United States at the British Library of Information, 5 East 45th St., New York. Price, 1/1/9; for the set 8/14/9.

THE ninth and last volume of this splendid system (for Reviews of other volumes see AM. J. MED. SCI., 1930, **179**, 120, 121; 1931, **180**, 718; 1931, **182**, 121, 271) by 27 authors is devoted to selected branches of general bacteriologic technique. On account of the vast field, the methods are arbitrarily selected without any discussion of principles or relative merits. The chief topics covered are the microscopic demonstration of bacteria, culture media and pH, cultivation of anërobes and spirochetes, isolation of single cells, viruses, bacteriophage, biochemical and serologic methods, oxidation-reduction, production of variants, general handling of laboratory animals. A general index of 68 pages completes this valuable volume.

E. K.

PHYSICIANS' MANUAL OF BIRTH CONTROL. By ANTOINETTE F. KONIKOW. Pp. 233; illustrated. New York: Buchholz Publishing Company, 1931. Price, $4.00.

THIS is a work that deserves wide circulation. The subject matter is well presented and the language clear, convincing, forceful; the arrangement good. It is really more than its modest title of "Manual" would infer. It is an excellent, but not too detailed, review of the whole subject of contraception, written from the practical viewpoint.

Part I deals with a general discussion of the urgent need of medically supervised contraception, exposes the absurdity of most of the current medical prejudices against it, and closes with a classification of all possible contraception methods.

Part II consists of a discussion, in order, of all the various methods employed, the author stating frankly her opinion of the merits and demerits of each.

Part III, in admirable detail, describes first the technique of the method the author prefers, then gives the reasons for the occasional failure, and lastly discusses the incalculable benefits of birth control from the psychic point of view.

Part IV is entirely statistical and, though of great interest, presents too small a series of cases to furnish material for dogmatic generalizations.

At the start of the book is a timely note for busy practitioners, telling them just where to turn for immediate practical information.

It is to be hoped that, through this book of Dr. Konikow's, the medical profession will avail itself of an opportunity for service to humanity hitherto rather neglected. O. T.

How's Your Blood Pressure? By Clarence L. Andrews, M.D., Attending Physician and Medical Chief at the Atlantic City Hospital. Pp. 225. New York: The Macmillan Company, 1931. Price, $2.50.

Along with diet, vitamins, ultraviolet light and cancer, blood pressure has become a major topic of discussion among the laity. Because of numerous misconceptions regarding the workings of the circulatory system, many have become victims of a "blood pressure psychology" which has almost attained the proportions of a "blood pressure hysteria." In this book, written for the layman, the author attempts to allay many of the fears incident to all the misdirected talk about blood pressure. He presents the subject in a pleasing style and in language that can be understood by laymen. Many examples are drawn from well known physical principles to clarify the elementary presentation of the physiology of circulation. The book ought to satisfy, at least in part, the natural desire of the intelligent layman to know more about his own body. A. C.

The Physiology of Muscular Exercise. By the late F. A. Bainbridge, M.A., M.D. (Cantab)., D.Sc., F.R.C.P., F.R.S., Professor of Physiology, University of London. Rewritten by A. V. Bock, M.D. (Harvard), Ph.D. (Cambridge), Assistant Professor of Medicine, Harvard; Physician, Massachusetts General Hospital, Boston and D. B. Dill, Ph.D. (Stanford), Assistant Professor of Biochemistry, Harvard. Pp. 272; 46 illustrations. Third Edition. New York: Longmans, Green & Co., 1931. Price, $5.00.

This revision of Bainbridge's monograph provides many interesting data for those interested in this field, and is a perfect mine of information. Much new material has been incorporated without lengthening the book to any great extent. On the other hand the clear descriptive style of Bainbridge has been lost, and, though the general form of the book is unchanged, it can no longer be described as easy reading.

For instance in regard to physico-chemical changes in the blood, readers are referred to L. J. Henderson's Silliman lectures, and though graphs are given, no real attempt is made to summarize this subject in simple language.

The statement is made that "nothing takes place in the serum that does not have a fairly simple interpretation" but the reader would never guess it. In other parts similar difficulties are encountered, apparently due to the same determination to conserve space.

The material is admirably up to date, and almost the only criticism that can be made is that the revisers have failed to discard completely the larger values for circulation rate obtained by modified Haldane methods in favor of the lower values given by acetylene and by Starr and Gamble's modified ethyl iodid methods. Their interpretation fluctuates somewhat between the two standards; the normal resting value is assumed as 5 to 6 liters per minute (p. 66) but later in considering the complementary value of oxygen utilization lower values for circulation rate (3 to 4 liters per minute) are considered valid (p. 130). H. B.

THE CONQUEST OF OLD AGE. By PETER SCHMIDT, M.D. Translated by EDEN and CEDAR PAUL. Pp. 307; 40 plates. New York: E. P. Dutton & Co., 1931. Price, $5.00.

EVER since the appearance of Steinach's *Verjüngung* in 1920, many have looked upon the idea of rejuvenation with scorn because of its connection with a revival of sexual powers. Humorists, columnists and even critics among medical men took up the theme and reduced it to absurdity with the result that what was truly scientific in the work of the Viennese scientist met with little appreciation. The author of "The Conquest of Old Age," a disciple of Steinach, addresses his book to both physicians and laymen. With all the enthusiasm of the specialist, he presents the facts as he sees them in the hope that Steinach's work will receive more widespread recognition. All the case histories presented show strikingly good results, but no claim is made for 100 per cent successes. No statistics are given because of the incompleteness of follow-up data, yet the author states that his various rejuvenation operations have yielded a higher percentage of good results during the last 2 years than H. Benjamin's 77 per cent successes reported in 1926.

At times, the author carries his enthusiasm a bit too far. For example, in discussing rejuvenation and its critics, he says, "People shrink from the extra work involved in the learning of new theories and the mastering of new practical methods. The general practitioner, moreover, is afraid lest there may no longer be a field for the application of much of his therapeutic knowledge and skill if all the disabilities of old age can be shuffled out of the world." This argument is obviously rather weak.

The reader who is interested in the rejuvenation controversy will find enough facts in the book to decide for himself. A. C.

A TEXTBOOK OF SURGERY. By JOHN HOMANS, M.D., Assistant Professor of Surgery, Harvard Medical School. Pp. 1195; 513 illustrations. Springfield, Illinois: Charles C Thomas, 1931. Price, $9.00.

IN a single large volume the author has attempted to present in textbook form, material which comprises the specialty of general surgery as taught at Harvard Medical College. Under "General Surgery" the author has grouped many of the branches of the so-called surgical specialties. Practically no operative technique is given. Though the substance has been furnished by a number of different individuals, yet the material has been condensed, correlated and apparently rewritten by the author-editor. This

results in a uniformity of presentation and style which is most commendable and worthy. It is only through the physical limitations of the book that it has failed to achieve its purpose of an authoritative text. Due to these limitations, much valuable material has been omitted. Undesirable curtailment has been resorted to. It cannot be said that the book is up to date, as in many instances the more recent advances of knowledge in various disease processes and forms of treatment are not mentioned. The book is printed on thin, light weight paper of poor quality, which creases and wrinkles easily. There are a number of line drawings, reproduced in black and white. These illustrations, due to lack of shading, are inartistic, though illustrative. In many instances, the illustrations remind one of the inferior woodcuts used in surgical texts of some 40 or more years ago. Though the book will probably enjoy a large sale because of the contributors, it will not challenge the supremacy of the texts of Da Costa, Ashhurst, or other present-day masters. G. W.

CRIPPLED CHILDREN. THEIR TREATMENT AND ORTHOPEDIC NURSING. By EARL D. MCBRIDE, B.S., M.D., F.A.C.S., Instructor in Orthopedic Surgery, University of Oklahoma, School of Medicine. Pp. 280; 159 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, $3.50.

THIS small book is written for the purpose of imparting orthopedic information and instruction to the nurse, parent and the social worker having to do with the care of the crippled child. The author, in so limiting the scope of his book, has created an almost impossible task. It is to be regretted that he has failed in this self-imposed task. The text is too brief and rudimentary to serve as a textbook for nurses. On the other hand, the material is presented in a too didactic and inelastic technical manner to be of much service to the social worker or parent. The material is presented in an almost barren outline form. The author's opinions are set forth in the form of unchangeable dicta. No attempt is made to present the views of those who do not agree with the author. There are many excellent photographic illustrations, a few Roentgen rays, and an occasional line drawing. The illustrations alone save the book from being worthless. It is impossible to recommend this treatise to those whom the author has attempted to reach. G. W.

SURGICAL PATHOLOGY OF PROSTATIC OBSTRUCTIONS. By ALEXANDER RANDALL, M.A., M.D., Professor of Urology, University of Pennsylvania. Pp. 266; 75 half-tones and 22 line engravings. Baltimore: Williams & Wilkins Company. Price, $7.00.

"AN analysis of 1215 autopsies studying especially 4 lesions of importance: hypertrophy, median bar, carcinoma and abscess."

Randall presents here the gross morbid pathology of "prostatism" as seen in the largest series of postmortem examinations as yet collected. This monograph is the first thorough attempt to classify macroscopic alterations occurring in the prostate gland, while previous authors have confined their researches to the etiologic and microscopic factors involved. If Randall's classification is accepted, which it well may be, a uniformity of nomenclature regarding prostatic pathology is possible that would eliminate the conflicting diagnoses and titles that are employed at present. Much confusion has existed heretofore in the literature regarding the classi-

fication of prostatic obstruction, especially the condition known as "prostatic bar." The author clearly differentiates the glandular bars, which are really hypertrophies of the posterior commissural tissue from the fibrous bars, which latter may be inflammatory in origin.

The illustrations are unusual in their excellent photography showing each condition in true size, so that accurate comparisons may be made between individual cases. A number of typical examples of each pathologic aspect are shown. Statistics as to age, race and type are presented in considerable detail including graphic charts.

This publication is most opportune as a contemporary writer claims that the gross changes such as found by Randall at autopsy do not exist as pathologic entities. The conclusions of Randall seem quite definite when supported, as they are, by numberous actual specimens.

This book should prove of interest both to the specialist and practitioner who is interested in the problem of vesical outlet obstruction. Prostatism has been recognized generally as an important element in many cardio-renal and vascular conditions and in this publication may be found the factors for urinary retention and bladder dysfunction. Randall's work is an authoritative and scientific presentation of facts that have been greatly needed to clear a heretofore poorly understood pathologic picture.

The plan of this monograph does not necessitate indexing, but a detailed index would be of great aid in locating readily the subject matter. A more detailed bibliography would facilitate in locating original references.

F. S.

MEDICAL ELECTRICITY FOR STUDENTS. By A. R. I. BROWNE, Member of the Society of Radiographers, Radiographer at the Royal Alexandria Infirmary. Pp. 245; 88 illustrations. Third Edition. New York: Oxford University Press, 1931. Price, $4.00.

THIS is an elementary textbook written, primarily, for physiotherapy technicians. In the text are discussed, briefly, various electrotherapeutic currents, their physical characteristics and mode of action as well as their methods of application and therapeutic indications. Various types of apparatus are also described and information given as to their construction and mode of employment. The static machine, however, is not mentioned and the chapter on high frequency and diathermy is entirely too brief to be of any value.

As a whole the little volume is capably written in a clear, comprehensible manner. It is a production that should be of considerable instructive value for beginners in the study of medical electricity.

J. N.

TRAUMATOTHERAPY. THE TREATMENT OF THE INJURED. By JOHN J. MOORHEAD, Professor of Surgery and Director, Department Traumatic Surgery, New York Post-Graduate Medical School and Hospital. Pp. 574; 625 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, $7.00.

HEREIN is contained a wealth of experience in the treatment of acute injuries. Each page is filled with valuable, practical material, clearly and concisely presented by the outstanding expert in this specialty. The Reviewer is unacquainted with any textbook that compares with Professor Moorhead's most recent work. "Traumatotherapy" should be the *vade mecum* of every industrial surgeon and of those general practitioners who are called upon to render emergency first aid.

G. W.

A LIFE OF JOSEPH PRIESTLEY. By ANNE HOLT. With an Introduction by FRANCIS W. HIRST. Pp. 221; 1 illustration. New York: Oxford University Press, 1931. Price, $3.50.

PRIESTLEY'S fame as a scientist, especially in connection with the discovery of oxygen, rests secure and his scientific progress can easily be followed in Thorpe's Life in the English Men of Science series. His theological, historical and even political activities, however, with which he personally was more intensely concerned, have received but scant attention; "it was thus with the object of rescuing Priestley's many-sided life from oblivion that this study was undertaken." The task has been well and pleasantly accomplished. Not only does a clear impartial picture of the man himself emerge, but also his dogmatic but rationalistic theology is seen preparing the way for the Higher Criticism of the next century and his radical philosophy marked real progress in pilosophic studies. The hostility that resulted in the destruction of his library and laboratory in Birmingham drive him in 1794 to the "sweet situation" and "delightful retreat" of Northumberland. This local color and the fact that his descendants still flourish in this country should add to his interest for Pennsylvanians. The exile enjoyed the friendship of Jefferson and many other intellectuals, while the American Philosophic Society went far to make up for the loss of the Royal Society at home. It is interesting to learn that he preferred the simplicity of his pioneer home to the professorship of chemistry at the University of Pennsylvania which he declined, though he was able frequently to cover the 130 odd miles to Philadelphia to preach religion and talk philosophy.

Three pages of Bibliography and Manuscript Sources increase the value of this work for Priestley's admirers, though it unfortunately is far from a complete list of the works from his pen. E. K.

BOOKS RECEIVED.

NEW BOOKS.

Publications of the Committee on the Costs of Medical Care: No. 14. The Costs of Medicine. By C. RUFUS ROREM, PH.D., C.P.A., and ROBERT P. FISCHELIS, B.S., PHAR.D. Pp. 250. Price, $2.50. *No. 16. The Healing Cults.* By LOUIS S. REED, PH.D. Pp. 134. Price, $2.00. Chicago: The University of Chicago Press, 1932.

Roentgenologic Studies of Egyptian and Peruvian Mummies. Anthropology Memoirs, Vol. III. By ROY L. MOODIE, Paleopathologist to the Wellcome Historical Museum, London. Pp. 62; 76 plates in photogravure, chiefly from roentgenograms. Chicago: Field Museum of Natural History, 1931. Price, $5.00.

The Expectant Mother's Handbook. By FREDERICK C. IRVING, A.B., M.D., Professor of Obstetrics, Harvard Medical School, etc. Pp. 203; 26 illustrations. New York: Houghton Mifflin Company, 1932. Price, $1.75.

Cancer: Civilization: Degeneration. By JOHN COPE. Pp. 293; 55 illustrations. London: H. K. Lewis & Co., Ltd., 1932. Price, 15/– net.

Clinical Interpretation of Laboratory Reports. By ALBERT S. WELCH, A.B., M.D., Clinical Instructor in Medicine in the University of Kansas School of Medicine in Kansas City, Kansas, etc. Pp. 366; 16 illustrations, 1 in color. Philadelphia: P. Blakiston's Son & Co., Inc., 1932. Price, $4.00.

Anaesthesia. By W. STANLEY SYKES, M.A., M.B. (CANTAB.), D.P.H. (LEEDS), M.R.C.S., Anesthetist to the General Infirmary at Leeds, etc. With a section on Local Anesthesia by P. J. MOIR, M.C., M.B. (GLASGOW), F.R.C.S. (ENG.), Hon. Assistant Surgeon, General Infirmary at Leeds, etc. Pp. 128; illustrated. New York: W. W. Norton & Co., Inc., n.d. Price, $2.00.

California's Medical Story. By HENRY HARRIS, M.D., Associate Clinical Professor of Medicine, University of California; Chief of Medical Department, San Francisco Polyclinic. With an Introduction by CHARLES SINGER, M.D., D.LITT., University of London, London, England. Pp. 421; illustrated. San Francisco: J. W. Stacey, Inc., and Springfield, Illinois: Charles C Thomas, 1932. Price, $7.00.

Practical Treatment of Skin Diseases. By EDUARD AHLSWEDE, M.D., New York and Hamburg, Formerly Assistant Physician, University Skin Department, Direction of Professor Unna, Eppendorf Hospital, Hamburg, etc. Pp. 770; 77 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, $12.00.

Human Cancer. By ARTHUR PURDY STOUT, M.D., Associate Professor of Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgical Pathologist, Presbyterian Hospital, New York. Pp. 1007; 331 illustrations. Philadelphia: Lea & Febiger, 1932. Price, $10.00.

Resultats du Traitement Chirurgical de l'Angine de Poitrine. By D. DANIELOPOLU, Professeur de Clinique Médicale a l'Université de Bucarest, etc. Pp. 285. Bucarest, Roumania: Impr. Cultura, 1932.

A valuable summary by a pioneer in this method, including 54 observations on the method of suppressing the presser reflex and 82 observations on sympathectomy (stellate ganglion).

Cerebral Injury in New-born Children Consequent on Birth Trauma; with an Inquiry into the Normal and Pathological Anatomy of the Neuroglia. By ERIK RYDBERG. Pp. 247; 49 illustrations. Copenhagen: Levin & Munksgaard, 1932.

Builders of American Medicine. Being a Collection of Original Papers read before the Victor C. Vaughan Society of the University of Michigan Medical School. Pp. 243; illustrated. Ann Arbor: George Wahr, 1932.

English-speaking Students of Medicine at the University of Leyden. By R. W. INNES SMITH, M.D., (EDIN.) With Foreword by JOHN D. COMRIE, M.D., F.R.C.P., (EDIN.), Lecturer on the History of Medicine at the University of Edinburgh. Pp. 258; 1 illustration. Edinburgh: Oliver & Boyd, 1932. Price 16/- net.

Medical Men in the American Revolution, 1775–1783. The Army Medical Bull., No. 25. By LOUIS C. DUNCAN, Lieut.-Colonel, U. S. Army, Retired. Pp. 414; 53 illustrations. Carlisle Barracks, Pa.: Medical Field Service School, 1931.

Diseases of the Coronary Arteries (Myocarditis). By DON C. SUTTON, M.S., M.D., Associate Professor of Medicine, Northwestern University, etc., and HAROLD LUETH, PH.D., M.D., Formerly Instructor of Physiology, Northwestern University, Chicago. Pp. 164; 42 illustrations, 3 colored plates. St. Louis: The C. V. Mosby Company, 1932. Price, $5.00.

Researches on Blackwater Fever in Southern Rhodesia. No. 6 of the Memoir Series of The London School of Hygiene and Tropical Medicine. By G. R. Ross, M.B., CH.B., PH.D., D.P.H., Rhodesian Research Fellow, London School of Hygiene and Tropical Medicine. Pp. 262; illustrated with tables and charts. London: The London School of Hygiene and Tropical Medicine, 1932. Price, paper, 8s; cloth, 10s. 6d.

Pain in the Pleura, Pericardium and Peritoneum. By JOSEPH A. CAPPS, M.D., Professor of Clinical Medicine, University of Chicago, with the collaboration of GEORGE H. COLEMAN, M.D., Assistant Professor of Medicine, Rush Medical College. A Foreword by ANTON J. CARLSON, M.D., PH.D., Chairman of the Department of Physiology, University of Chicago. Pp. 99; 33 illustrations. New York: The Macmillan Company, 1932. Price, $3.00.

The Heart Rate. By ERNST P. BOAS, M.D., Associate Physician, Mt. Sinai Hospital, New York City, and ERNST F. GOLDSCHMIDT, PH.D., Research Fellow (1930–1931), Department of Surgery in the Yale University School of Medicine. Pp. 166; illustrated with figures and charts. Springfield, Illinois: Charles C Thomas, 1932. Price, $3.50.

Medicine Among the American Indians. Vol. VII of Clio Medica. By ERIC STONE, M.D. Pp. 139; 17 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, $1.50.

Recent Advances in Pathology. By GEOFFREY HADFIELD, M.D., F.R.C.P. (LOND.), Professor of Pathology in the University of London; Pathologist to the Royal Free Hospital, and LAWRENCE P. GARROD, M.A., M.B., B.CH. (CAMB.), M.R.C.P. (LOND.), Bacteriologist and Lecturer in Bacteriology, Late Demonstrator of Pathology, St. Bartholomew's Hospital. Pp. 392; 67 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1932. Price, $3.50.

Zur Kenntnis des Einflusses der Graviditaten und des Ergosterins auf das Wachstum. By VON ERIK AGDUHR, Upsala. Pp. 82; illustrated. Upsala: Almqvist & Wiksells Boktryckeri-A.-B., 1932.

Robert Koch. I. Teil 1843–1882. By BRUNO HEYMANN, A. O. Professor an der Universität zu Berlin. Grosse Männer Studien zur Biologie des Genies. Herausgegeben von Wilhelm Ostwald. Zwölfter Band. Pp. 353; illustrated. Leipzig: Akademiscke Verlagsgessellschaft m.b.H., 1932. Price, paper, 16 M; bound, 18 M.

The Surgical Clinics of North America, Vol. 12, No. 3 (Lahey Clinic Number, June, 1932). Pp. 299; 123 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, paper $12.00; cloth, $16.00.

Electrosurgery. By HOWARD A. KELLY, M.D., LL.D., F.A.C.S., Baltimore, and GRANT E. WARD, M.D., F.A.C.S., Baltimore. Pp. 305; 382 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $7.00.

A Series of Original Dry-point Portraits of British Medical Scientists. By A. WATSON TURNBULL, 21 Sheen Road, Richmond, Surrey, England. Price, £5.5.0 each.

This is an attractive set of dry-point portraits of such famous British medical scientists as Lord Lister, Sir J. Y. Simpson, Sir James Paget, Sir Patrick Manson, Sir Arthur Keith, and Sir Ronald Ross. The edition is limited to 25 signed and numbered artist's proofs from each plate which is to be destroyed. The plates are 11 inches high by 9 inches wide, giving a head about 4 inches high.

Minor Surgery of the Urinary Tract. Mayo Clinic Monograph. By HERMON C. BUMPUS, JR., PH.B., M.D., M.S. in Urology, F.A.C.S., Associate Professor of Urology, The Mayo Foundation. With a chapter on Carbuncles by JOHN L. CRENSHAW, M.D., Associate Professor of Urology, The Mayo Foundation, and chapter on Postoperative Care by ANSON L. CLARK, M.E., M.D., Section on Urology, The Mayo Clinic. Pp. 124; 57 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $3.00.

Collected Papers of The Mayo Clinic and The Mayo Foundation, Vol. XXIII, 1931, Published, May, 1932. Edited by MRS. MAUD H. MELLISH-WILSON and RICHARD M. HEWITT, B.A., M.A., M.D. Pp. 1231; 265 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $13.00.

The usual wide range of topics is covered in this fine volume of 191 articles by those on or connected with the Mayo staff. There are also included 124 papers by title and reference. Sub-sections are: Alimentary Tract; Genito-urinary Organs; Ductless Glands; Blood and Circulatory Organs; Skin and Syphilis; Head, Trunk and Extremities; Brain, Spinal Cord and Nerves; Technic; Miscellaneous.

NEW EDITIONS.

Lang's German-English Dictionary. Revised and Edited by MILTON K. MEYERS, M.D., Neurologist to the Northern Liberties Hospital; Chief of Nerve Clinic, St. Agnes Hospital; Consulting Neurologist, Jewish Hospital, Philadelphia, etc. Pp. 926. Fourth edition, enlarged. Philadelphia: P. Blakiston's Son & Co., Inc., 1932. Price, $10.00.

Just as a knowledge of German is essential to the proper study of medicine, so an excellent dictionary like this is essential both in helping with difficult passages and in giving exact meanings to difficult words. Much space could be saved by omitting the repetition on each page of 3 lines of pronunciation examples.

The Mongol in Our Midst. By F. G. CROOKSHANK, M.D., F.R.C.P. Pp. 539; illustrated. Third edition, greatly enlarged and entirely rewritten. London: Kegan Paul, Trench, Trubner & Co., Ltd., 1931. Price, 21s. net.

Special Cystology. By various contributors. Edited by EDMUND V. COWDRY, Washington University, St. Louis. Pp. 1838; illustrated. Second edition. Three volumes. New York: Paul B. Hoeber, Inc., 1932. Price, $30.00.

A Text-book of General Physiology. By PHILIP H. MITCHELL, PH.D., Professor of Physiology at Brown University. Pp. 799; 196 illustrations. Second edition. New York: McGraw-Hill Book Company, Inc., 1932. Price, $6.00.

As compared with the first edition (1923) "the second edition differs radically in that much less space has been given to the biochemical aspects of physiology in order to make room for more physical chemistry as applied to physiology. To this end several of the earlier chapters have been eliminated or condensed, and four entirely new ones, Surface Action, The Colloidal State, Diffusion and Osmosis, and The Permeability of Cells, have been added."

A Manual of Pharmacology. By TORALD SOLLMAN, M.D., Professor of Pharmacology and Materia Medica in the School of Medicine of Western Reserve University, Cleveland. Pp. 1237. Fourth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1932. Price, $7.50.

The following sections have been largely rewritten: Arsphenamin fate—Barbiturates—Bismuth—Cinchophen toxicosis—Gold—Iodin compounds in roentgenography—Liver extract—Mercury—Morphin addiction; fate; peristalsis—Nitric vapors—Pituitary—Quinin and plasmoquin—Sexual hormones—Temperature regulation—Thallium—Vitamins. The main purpose of the book—to furnish an outline of the current conception of the actions of drugs—has been well maintained.

Materia Medica, Pharmacology, Therapeutics and Prescription Writing. By WALTER A. BASTEDO, PH.G., M.D., SC.D. (HON. COLUMBIA), F.A.C.P. Pp. 739; 78 illustrations. Third edition reset. Philadelphia: W. B. Saunders Company, 1932. Price, $6.50.

"New articles have been added on suprarenal cortex, ephedrin, quinidin, plasmochin, yatren, ethylene, the barbiturates, pre-anesthetic narcotics, carbon dioxid, carbon tetrachlorid, the antiseptic dyes, mercurochrome, metaphen, the mercury diuretics, phenylhydrazine, insulin, ovarian preparations, colloidal lead in cancer."

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Relationship Between Liver Injury Induced by Alcohol and Elimination of Phenolsulphonephthalein.—DEB. MACNIDER and DONNELLY (*Proc. Soc. Exper. Biol. and Med.*, 1932, **29**, 586) mention that in previous communications they recorded a rather bizarre series of results obtained from the injection of phenolsulphonephthalein in dogs poisoned by ethyl alcohol. In some of these animals there would be a reduction in the output of dye lasting throughout the course of experiments; in another group the dye eliminated would be only slightly affected, whereas in the third group an occasional animal developed albuminuria with casts and every symptom of nephritis, yet the elimination of the dye would rise 20 to 30 per cent. An explanation of these unusual results is suggested in some recent contributions from Whipple, *et al.* Dr. MacNider therefore investigated histogically the livers of animals intoxicated by alcohol in which there was considerable increase in the phthalein elimination in spite of the clinical evidence of nephritis. There was present marked liver injury involving first the periphery of the liver lobule and extending inward toward the central vein. This produced an extensive process with areas of degeneration showing marked cloudy swelling of the liver cells. The nuclei also showed a considerable accumulation of stainable lipoid material. The intertubular capillaries were distended with blood but no hemorrhage into the liver substances was observed, nor was there any increase in connective tissue. The control animals which showed diminished elimination of phthalein had not any of these characteristic changes in the liver lobules. These pathologic studies substantiated the hypothesis that in the presence of liver injury and renal disease the excretion of phthalein may be high as a result of decreasing the amount of dye excreted by the liver and intestines or else by a lowering of the ability of the liver to destroy the substance.

SURGERY

UNDER THE CHARGE OF
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Intermittent Gastric Ileus Due to Mechanical Causes.—MEYER and SINGER (*Surg., Gynec. and Obst.*, 1931, **53**, 742) say that a clinical syndrome consisting of pain in the upper abdomen, vomiting of gastric contents, distention of the stomach and pyloric obstruction as determined radiologically is referred to as gastric ileus. When caused by a mechanical condition which obstructs interruptedly, the designation intermittent gastric ileus of the mechanical type is applied. Personal experience has been had with four etiologic factors. The most important is the benign pedunculated gastric tumor which acts as a ball valve by prolapsing into the pyloric ring or which incites vigorous peristalsis, leading to intussusception of the stomach into the duodenum. A cauliflower carcinoma with a pedicle located just proximal to the pylorus illustrates the second type of mechanical cause of periodic obstruction to the gastric outlet. The third etiologic factor discussed is a gastrolith derived from powders used in the Sippy treatment for ulcer. A coëxisting pyloric stenosis prevented the passage of the concrement and occasioned intermittent impaction. The fourth and most unique type of cyclic obstruction was due to an anomalous redundant fold of prepyloric mucosa which, acting like an epiglottis, produced a discontinuous occlusion of the pylorus. Other mechanical causes of intermittent gastric ileus might be added to the ones illustrated and discussed. The object of the publication primarily is to direct attention to a clinical syndrome which permits recognition of hitherto obscure conditions that lend themselves admirably to surgical cure.

Bacterial Synergism in Disease Processes.—MELENY (*Ann. Surg.*, 1931, **94**, 961) believes that certain bacteria have a synergistic function in the production of certain types of disease or symptoms of disease. This synergistic action should always be kept in mind in studying disease processes involving tissues, organs or systems in which mixtures of organisms are frequently or occasionally found. The author has made observation of the hemolytic synergism of two organisms found in the exudate in a case of chronic empyema; of the lethal effect in experimental animals of a mixed culture of organisms found in unsterile catgut which could not be produced by the same organisms in pure culture; of the adjuvant action of organisms found in cases of peritonitis demonstrated by the production of death with small fractions of minimal lethal doses of these organisms when injected together; of the almost exact duplication of bacteriologic findings in 2 cases of progressive gangrene of the abdominal wall following the drainage of a peritoneal abscess. These cases both yielded a micro-aërophilic streptococcus and a Staphylococcus aureus capable of producing a gangrene of the skin and subcutaneous tissues when injected together into experimental animals, while the pure cultures failed to produce the lesion.

THERAPEUTICS

UNDER THE CHARGE OF

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Diet as a Prophylactic Agent Against Puerperal Sepsis.—If vitamin A has any therapeutic effect in septicemia, its value as a prophylactic agent should be even greater. Experimental work on young animals has suggested that vitamin A and carotene act as "anti-infectives" because if they are absent from or deficient in the diet, multiple foci of infection develop. The preventive and curative effects of vitamin A and carotene in the autogenous sepsis of the animals were equally great. GREEN, PINDAR, DAVIS and MELLANBY (*Brit. Med. J.*, 1931, p. 595) now report a study of the prophylactic action of vitamin A against puerperal sepsis in women. Substances essential for the growth of the embryo are obtained either from the food or from the body of the mother. The body, particularly the liver, can store considerable amounts of the vitamin A obtained from food. A depletion of this stored vitamin may well occur in certain cases of pregnancy. The reported study comprises 275 women treated with the vitamin preparation and 275 alternate cases which served as controls. All cases were delivered in the hospital. The women were instructed to take the preparation 1 month previous to the calculated day of labor. The preparation "radiostoleum" which was used contained vitamins A and D dissolved in a neutral oil; 1 cc. containing 150 "blue units (Carr and Price)" of vitamin A and 5000 units of vitamin D in the form of irradiated ergosterol. The women took one-half a teaspoonful of the preparation. In the group which took the vitamin preparation, there were only 3 cases of puerperal sepsis (1.09 per cent); in the control group there were 13 morbid cases (4.73 per cent). This difference was twice the standard error. The morbidity rate for the two groups combined was much lower than that of previous years. The total number of cases with pyrexia was 56 in the vitamin group and 98 in the control group. The difference is almost four times the standard error. The degree and duration of pyrexia was also greater in the control group than in the vitamin group. Twenty-six cases in the vitamin group and 27 in the control group were subjected to manual or instrumental intervention of a major kind. None of the vitamin group developed local infection, but 6 of the control group did. The authors believe that these results indicate that the administration of vitamin A during the last month of pregnancy diminishes the liability to a morbid puerperium. On experimental grounds, the authors claim that vitamin D possesses

little anti-infective action. Antenatal care should always include a diet rich in natural sources of vitamin A. Milk, egg yolk, green vegetables, carrots and butter should be taken unsparingly. Mammalian liver is also an excellent source of vitamin A. A well-varied natural diet of this kind also supplies adequate amounts of the vitamins B, C and D and the calcium, phosphorus, iron, copper, manganese and iodin essential for the pregnant women. If the diet has to be supplemented, cod-liver oil is the cheapest source of vitamins.

The Effectiveness of Follicular Hormones Administered Orally.—The majority of hormones of internal secretion are ineffective, or only slightly effective, when given orally as compared with parenteral administration. So far as the follicular hormone is concerned, the ratio of effectiveness between parenteral and oral administration varies, according to the literature, from 1 to 2.5 (Dohrn) to 1 to 100 (Laqueur). Furthermore, Allen and Doisy deny the effectiveness of this hormone on oral administration. Such a wide discrepancy may be the result of different methods of standardization or preparation of the hormone. SCHOELLER, DOHRN and HOHLWEG (*Wien Arch. f. inn. Med.*, 1931, **21**, 323) have now reinvestigated this problem using preparations of varying physiologic potency. The preparations were administered orally to castrated female rats in a watery solution of 1.2 cc. volume. The results clearly indicate that the purer the preparation, the larger the amount required to induce estrus in animals. Thus relatively the largest amount of the crystallized hormone was required to produce estrus. The authors conclude that certain impurities accompanying the pure hormone probably increase absorption or protect the hormones from the action of other substances. Another series of experiments indicates that the same amount of follicular hormone is more effective if administered in several divided doses.

PEDIATRICS

UNDER THE CHARGE OF

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Symptoms in Congenital Lesions of the Heart that Permit Venous Shunting.—LEECH (*Am. J. Dis. Child.*, 1932, **43**, 1086) studied 62 patients with congenital heart disease, found at postmortem, of such a nature as to permit venous shunting. He attempted to determine the presence or absence of characteristic symptoms and signs. Nearly half of these patients presented no clinical abnormalities referable to the circulatory apparatus. While the incidence of cyanosis, periodic as well as constant, was found to be somewhat higher in this group than among 20 other patients whose autopsies revealed congenital defects of the heart that did not permit of venous shunting, this sign was found not to differentiate sufficiently the two general types of lesions. Eight, or about 13 per cent, of the large group presented a syndrome

that was almost totally absent in the smaller group with the nonvenous shunt type of defect. In the larger group, 5 additional patients presented convulsive seizures not accompanied by cyanosis and respiratory distress. When other causes, such as pneumonia, epilepsy, meningitis and severely toxic conditions, can be ruled out and when the patient is known to have congenital heart disease, the occurrence of convulsive-like seizures, often epileptiform in character, sometimes followed by drowsiness and frequently accompanied by hyperpnea, may justly be interpreted as an indication of a lesion, or a combination of lesions, that permits venous shunting, especially if the patient shows a constant cyanosis, no matter how slight, or if the attack is accompanied by deep cyanosis.

Infantile Diarrhea.—POOLE, COOLEY and ELLWART (*Am. J. Dis. Child.*, 1932, **43**, 1101) found that infants in whom acute diarrhea developed late in the summer showed an intoxication after a variable length of time when improperly or inadequately treated. The intoxication is the result of several factors—anhydremia, acidosis and bacterial toxins, the last occurring particularly when the intestinal tract has been invaded by such organisms as the bacillus of dysentery or streptococci. Patients with such a condition require prompt and energetic treatment in order to save their lives. During this critical period their chief requirement is water. They feel that each patient should be individualized. It is recommended whenever it is possible to avoid hospitalization after the most acute period is passed in order to avoid the virulent bacteria that may be present in a hospital ward. Unsweetened evaporated milk, diluted to one-half or two-thirds strength, with protein or carbohydrate additions, proved to be a satisfactory formula for most of the patients in this series as soon as they were able to take milk. A certain amount of discretion must be used in each case because of the degrees of variation found in the hydrogen ion concentration of the stomach contents and in the individual child's reaction to food. The evaporated milk formulas can be readily adjusted in percentage acidity and consistency to meet these special requirements.

The Incidence of Respiratory Infections During the First 5 Years of Life.—MCLEAN (*Arch. Pediat.*, 1932, **49**, 279) made an intensive study of 1408 respiratory infections seen in 156 children in an attempt to find evidence of a periodic recurrent disease. A small number of children were included in this study so that all the patients were in intimate contact with the observer and were seen in practically all of their illnesses. A comparison of the average number of respiratory infections per patient and the average number of months per infection in the children with various groupings of the same age and length of observation, showed a marked consistency. During an exact period of 4 years from the date of birth in 86 and 70 children, 692 and 563 respiratory infections were seen. The average number of days between infections in the two series were 181.4 and 181.5 days. The average number of respiratory infections per patient in each series was 8.04 infections. The percentage of mild and severe infections in the two series was the same, 41 per cent mild and 59 per cent severe. Eight hundred and

forty-five respiratory infections were seen in 86 children observed for an exact period of 5 years from the date of birth. The children were placed in two groups of 43 patients. One group had 416 infections and the other 429, a difference of only 13 infections. In 70 children observed for an exact period of 4 years from birth 563 infections were seen. The patients were placed in two groups of 35 each. One group had 285 infections and the other 278, a difference of only 8 infections. In 140 children observed for an exact period of 4 years from date of birth, 1125 infections were seen. When the patients were placed in two groups of 70 children each, one group had 563 infections and the other 562 infections, a difference of only 1 infection. The monthly seasonal incidence of occurrences in 845 respiratory infections seen in 86 children observed for an exact period of 5 years from date of birth, compared with 563 respiratory infections seen in 70 children over an exact period of 4 years from birth, showed a definite consistency. Removal of tonsils and adenoids apparently had very little effect on either the number of or severity of respiratory infections. The consistency in the sameness of the total number of respiratory infections seen in various groupings of the same age, number and length of observations showed evidence of a periodic recurrent disease.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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The Treatment of Neurosyphilis.—SOLOMON (*Urol. and Cutan. Rev.*, 1932, **36**, 223) summarizes his experience in the therapeutic management of three types of neurosyphilis, namely, paresis, tabes and cases with predominantly meningeal symptoms. In paresis eminently satisfactory results are obtainable in approximately 30 per cent of cases, either with tryparsamid or fever therapy alone, but the author believes that the most satisfactory results are obtained by a combination of these two methods. It seems logical to begin with the simpler method, namely, tryparsamid; but, if after 2 or 3 months, progress is slow or unsatisfactory, a change to fever therapy is indicated. Conversely, the patient given a course of fever at the outset of treatment should be continued on tryparsamid to the point of complete serologic cure. The author believes that malaria is the most effective type of fever therapy and typhoid vaccine the least effective. Diathermy would seem to be equally as effective as malaria. In tabes tryparsamid would seem to offer the best means of treating the majority of cases. Intraspinal therapy as well as fever therapy are sometimes of spectacular benefit in cases nonresponsive to tryparsamid. The latter drug at times, supple-

mented with arsphenamin and bismuth, produces serologic negativity and symptomatic relief in the vast majority of cases. The time required for serologic cure, however, varies from months to years. Some patients show progression in their disease despite any type of treatment now in use. In the meningeal type of neurosyphilis the author again highly recommends the use of tryparsamid, which is said to act almost, if not entirely, as a specific drug. Clinical improvement is usually prompt and serologic cure occurs within the first year. There are some cases, however, that take very prolonged treatment to obtain serologic reversal to negative. The author has had no personal experience with fever therapy in this phase of neurosyphilis, but is led to believe by logic as well as the experience of others that it would be effective. In summarizing, the writer pleads for a more intensive study of the syphilitic patient from the standpoint of spinal fluid findings, for when changes characteristic of central nervous system invasion occur in the spinal fluid, the effect of treatment on the spinal fluid formula must be given first place in the subsequent treatment of the patient.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Rare Ovarian Tumors.—The pathology of three rare ovarian tumors has been presented by MEYER (*Am. J. Obst. and Gynec.*, 1931, **22**, 697) of Berlin in an interesting paper read before the American Gynecological Society. The first type of tumor he has called "disgerminoma," although it is often called "seminoma ovarii" because of its histologic similarity to the so-called seminoma of the testis. It is carcinomatoid in character since it consists of large epithelial cells. He has seen 27 cases of this type and has observed that these neoplasms are seen very often in pseudohermaphroditic individuals, but they are also seen in women with typically female bodies. The external genitalia and uterus are apt to be infantile in character, while in men such tumors are apt to be associated with cryptorchidism and poorly developed testicles. One of the striking features of this type of neoplasm is the early age of appearance, usually in the second or third decade. The author believes that they arise from an undifferentiated form of germinal cells which have lost their faculty of becoming either masculine or feminine in type and therefore can develop into identical pathologic structures in both types of sex glands. As these tumors originate from undifferentiated sex cells they necessarily will be void of any specific hormonal influence and thus fail to exert a specific stimulation for development of the secondary sex characteristics. They neither masculinize nor feminize the individual. They may attain enormous size and thereby

destroy the ovary and even the uterus, but if operated upon, the prognosis is good. The second type of tumor discussed is the granulosa cell tumor which may occur as a folliculoma, often associated with cysts; as solid masses or in thin cords or tubules; or as a diffuse structure resembling sarcoma. He believes that these tumors arise from undifferentiated cells and not from epithelial cells of the true follicle. They occur most frequently in women over 60 years of age in whom the ovary no longer contains follicles, so that it is impossible to think of their origin from follicle cells. Of 33 cases of this type studied by the author 1 died soon after the operation and only 3 from later metastases, 19 remaining permanently cured for varying periods of time ranging from 1 to over 4 years. In 27 of the cases bleeding was an important symptom. The endometrium was found frequently to be hyperplastic and the uterus enlarged. After removal of the tumor abnormal bleeding stopped and, in younger individuals, if not all the ovarian tissue was removed menstruation again became normal. He concludes that hypertrophy of the uterus was caused by the ovarian neoplasm, especially in those patients past the menopause. The third type of tumor presented is the arrhenoblastoma, which tends to cause women previously exhibiting normal female characteristics to take on those typical for the male sex. In these patients there is falling of the hair, deposits of fat, atrophy of the breasts, shrinkage of the opposite ovary and atrophy of the uterus with consequent amenorrhea and sterility. At the same time positive signs of masculinization appear such as male hirsuties, growth of a beard, enlargement of the clitoris and hypertrophy of the larynx with the development of a male voice. After removal of such a tumor the woman returns more or less fully to her former feminity, menstruation reappears and even pregnancy may occur. On the other hand, the signs of masculinity return with a recurrence of the growth. He believes that these tumors originate from undifferentiated germ cells which are not utilized during embryonic development but retain their sexual potency and proliferate later in life, exerting their influence in the direction toward masculinity. Patients afflicted with any of these three rare tumors are cured by operation in most instances without removal of the opposite ovary if it is unaffected.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Concerning Certain Aspects of the Fundus of the Eye in Arterial Hypertension.—BAILLART (*Bull. de la Soc. d'Ophtalmologie de Paris*, October 18, 1930) thinks that in the main, patients with hypertension, even if they have retinal lesions, have good vision unless the macula

is affected. Even before the retina is visibly affected, they may complain of a transparent haze, black or luminous spots or balls of fire before the eyes; and they may have transient spells of loss of vision due to vascular spasms in the retina or in the occipital lobe. In patients with such symptoms, the retinal arterial pressure will be found to be elevated. The onset of retinal lesions in a patient with hypertension indicates a failure of compensation on the part of the kidneys, the viscera, or the vessels. Extensive retinitis, with edema of the disks, hemorrhages and fibrinous exudates, can occur in hypertensive disease while the kidneys are still normal and while the retinal vessels are anatomically normal. It is difficult to differentiate ophthalmoscopically the retinitis of hypertension from the retinitis of nephritis. Punctate exudates are usually present in the peripapillary region in the retinitis of nephritis, and usually absent in the retinitis of hypertension. In the retinitis of nephritis, as pointed out by Abrami, Gallois, and Sthelin, the retinal arterial blood pressure rises disproportionately to the general systemic blood pressure. These authors think that this relative increase of blood pressure in the retina indicates a more severe type of hypertensive disease with greater liability to renal complications and that it is associated with increased intracranial pressure. It is true that the retinitis of nephritis can be improved in some cases by spinal puncture. In 12 cases in which the ratio of retinal to general blood pressure was normal (45 to 100), the urea in the blood was essentially normal. In 8 cases in which this ratio was increased (75 to 100), the blood urea percentage was definitely elevated. Apparently, the relative rise of retinal arterial pressure is more marked in cases of hypertension with impaired kidney function, and is thus of diagnostic and prognostic importance. An increase in the ratio of retinal to general arterial pressure may be caused by inflammation, by increased intracranial or by a local vascular lesion in the retina. Increased intracranial pressure is present in certain cases of hypertension and may lead to the erroneous diagnosis of brain tumor. If the central artery of the retina is obliterated by anatomic lesions or by spasm above the level of the papilla, the retinal blood pressure will be relatively low. If the obliterative process involves the vessels or capillary bed peripheral to the artery examined, the blood pressure will be relatively increased. Such lesions in the small arteries are frequent in hypertension and give rise, through ischemia, to the advanced forms of albuminuric retinitis. The elevation of local blood pressure in the retina is then not always a sign of increased intracranial pressure. Its serious prognostic significance rests rather upon the severe vascular disease that it indicates. Baillart concludes that the appearance of retinal lesions in arterial hypertension is the sign of a serious involvement. The purely hypertensive retinitis and the so-called albuminuric retinitis are quite similar, the latter differing only in the fact that the extravasation into the retina is serum made toxic by renal insufficiency.

Fundus Manifestations in Metabolic Diseases.—CAMPBELL (*Canad. Med. Assn. J.*, 1929, **21**, 530) finds that patchy contraction of the blood column is an indication of internal sclerosis. Widening and burnished-copper appearance of the central light streak occurs in medial sclerosis.

With these signs of sclerosis are associated changes at the arteriovenous crossings. Superficial, flame-shaped hemorrhages may be seen if hypertension accompanies the sclerosis. Sometimes round, punctate hemorrhages are found. Sclerosis of the vessels of the choroid may also be associated. In diabetes, retinitis never occurs in the young and is apparently related to the duration rather than to the severity of the disease. The changes may vary from fine, rounded, yellowish-white, solid masses around the macula to a picture resembling the retinitis of nephritis. The earlier lesions are susceptible to insulin and dietetic treatment. The more severe lesions are not improved by insulin though they do not contraindicate its use. Lipemia retinalis, on the other hand, is seen only in young diabetics in acidosis or coma. It clears up rapidly under insulin therapy. Nephrosis shows no fundus lesions. In septic focal nephritis, a few white areas of degeneration and hemorrhages, usually with a white center, may be seen. In about 10 per cent of cases of acute glomerulonephritis papilledema, cotton-wool exudates and hemorrhages occur. In the subchronic stage of parenchymatous nephritis, if the blood pressure is unusually high, hemorrhages and edema of the retina and disk may appear. The fundus changes in the nephritis of pregnancy resemble those seen in acute glomerulonephritis but are usually more extensive. The grade of edema may be great enough to cause detachment of the retina. Reattachment may occur; but further degenerative changes may seriously reduce vision. Early fundus changes are favorably influenced by therapeutic abortion; the late are not. In about 70 per cent, renal injury, and perhaps eye changes, will recur in subsequent pregnancies. In chronic glomerulonephritis, the retinitis is characterized especially by snow-bank exudates, hemorrhages, macular star, and anemia. Advanced renal insufficiency is present and is essential to the development of the retinitis. Death occurs within 1 or 2 years. Retinal vascular sclerosis is present before the onset of the retinitis and advances rapidly in its presence. The retinitis of malignant hypertension is characterized by hyperemia and edema of the disks, cotton-wool patches, and a fine macular star in the presence of marked contraction of the arteries and arteriosclerosis, usually not of the intimal type. This type of retinitis indicates a widespread vascular lesion and the life expectancy of these patients is short even if the renal function is satisfactory. Few other metabolic diseases show characteristic fundus changes. The spontaneous arterial pulsation seen in hyperthyroidism is an interesting exception.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Physiology of Drainage of Nasal Mucus. I. The Flow of the Mucous Currents Through the Drainage System of the Nasal Mucosa and Its Relation to Ciliary Activity.—The basic and ancillary sciences of medicine are not equal, nor is their rank of importance fixed. Con-

trariwise, like everything in Nature, their relative position in the scale is in a flux that is determined chiefly by the current demands of the march of Progress. While it is true, as HILDING (*Arch. Otolaryngol.*, 1932, **15**, 92) says, that "rhinologists seem to have neglected the subject" (nasal ciliary activity and mucinous secretion), it is also true that otorhinolaryngology's renaissance challenges in fervor and scope that of any other departmental branch of medical practice and science. Long since have the laboratories for physiology, pharmacology, chemistry, pathology and bacteriology supplanted the dissecting room and the tool-maker's shop as the training ground in otolaryngology. This is as it should be. The author's report is based on a study of the flow of nasal secretion in 31 persons, on various portions of whose Schneiderian membrane dots of India ink were placed. No ciliary activity could be demonstrated in the anterior third of the nose, which drains largely through the inferior and middle meatuses. The mucosa posterior to this region exhibited active ciliary motion especially in those areas least exposed to the flow of the inspired air. Furthermore, the protective layer of mucus covering all intranasal surfaces is continuous with that in the pharynx and esophagus, and moves in a manner not unlike an intact membrane, being motivated by ciliary movement and traction. In its posterior two-thirds the nose may be said to have a new lining about six times an hour; and approximately once an hour in its anterior one-third. Drainage from the anterior inactive areas required an hour or more, in contrast to from 3 to 10 minutes in the posterior, active areas. Generally speaking, the course of ciliary movement is toward the nasopharynx.

Infections of the Throat Due to Hemolytic Streptococci and Their Relation to Arthritis and Arthralgia. I. Observations With Particular Reference to Streptococcus Epidemicus of Septic Sore Throat.—Purposing "to bring forth the importance of hemolytic streptococci from infections of the throat in certain arthritic manifestations and to emphasize the possible rôle of hypersensitiveness to these organisms." PILOT (*Arch. Otolaryngol.*, 1932, **15**, 71) refers to former personal findings indicating that in routine cultures hemolytic streptococci occur in the throats of 61 per cent of persons and almost 97 per cent of excised tonsils; whereas Streptococcus epidemicus was found in the throat in less than 1 per cent (4 of 500 persons); and 3 of the 4 carriers of these streptococci had arthritic symptoms; and from the excised tonsils in 13.8 per cent (70 of the 506 pairs of tonsils) in 23 of which arthritis or arthritic pains were cited as the cause for removal, in addition to a history of sore throats. The author states that (1) arthritis and arthralgia may complicate scarlet fever, erysipelas, wound infections and sore throat due to hemolytic streptococci (2); that the development of the arthritis 3 or more weeks after the onset of the streptococcic infection suggests hypersensitiveness as an important factor; (3) that Streptococcus epidemicus of septic sore throat may be responsible for a relatively small number of cases of the rheumatic arthritis; (4) that the persistence of Streptococcus epidemicus is often associated with arthritis; and, finally, that tonsillectomy terminates the carrier state, and the associated arthritis frequently disappears.

RADIOLOGY

UNDER THE CHARGE OF
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The Roentgen Ray in the Diagnosis and Prognosis of Upper Urinary Tract Infection.—In the roentgenologic study of the kidney PLAGGEMEYER and WELTMAN (*Radiology*, 1932, **18**, 23) regard roentgenoscopic pyelography as essential. By this method overfilling of the pelvis and consequent pain to the patient can be avoided. Obscure details can be studied better than in the pyelograms. Under vision the kidney can be palpated and its mobility and the relation of calculi, tumors, etc., can be noted.

Air and Gas in the Soft Tissues.—Air and oxygen in the soft tissues occur in connection with compound fractures, gunshot injuries, lacerated wounds, surgical emphysema and after local treatment with hydrogen peroxid. Gas bacillus infection occasionally complicates injuries and accidents. RHINEHART (*Radiology*, 1931, **17**, 1158) holds that the earliest positive diagnostic finding is the demonstration on roentgenograms of the shadow defects produced by the gas. If made within 10 days of the accident every film of an injury in which the skin is damaged or broken, including the open reduction of fractures, should be carefully examined for evidences of gas. The conclusions from Roentgen ray examination are also of importance in selecting and directing the treatment of gas infections.

The Hilus of the Lung in the Child.—The roentgenologic diagnosis of tuberculosis of the bronchial glands is not made as often as it should, especially in children, according to ALTSCHUL (*Radiology*, 1931, **17**, 1147). A hilus showing increased density, whether hemogeneous or mottled, is always suspicious. Inequality of the hilar shadows is decisive for the diagnosis. In the majority of cases any enlargement of the glands is due to tuberculosis. In cases that are not recent a primary focus in the lung can usually be demonstrated. If a primary focus cannot be demonstrated one should recall that other infectious processes may give rise to glandular enlargement.

Influence of Ultraviolet Rays on Pharmacologic Potency of Digitalis.—Tincture of digitalis was irradiated with mercury vapor quartz lamps, with Roentgen rays and with radium by MACHT (*Arch. Phys. Therap., X-ray and Rad.*, 1932, **13**, 5). Irradiation with ultraviolet rays for short periods of time produced a deterioration or weakening in the pharmacologic potency of the tincture, as tested on living plants and animals. On progressive and prolonged exposure to ultraviolet rays, a point was reached where the photochemical changes resulted in the

formation of products exhibiting a greater toxicity for both plants and animals. This stage, on still further exposure, was followed by a secondary weakening in the pharmacologic potency of the irradiated tincture. The shorter ultraviolet rays, particularly those transmitted through a chlorin-bromin gas filter, were more effective than the longer rays in producing the changes described above. Exposure to Roentgen rays, to radium and to radium emanations resulted in a product which was greatly reduced in its activity for the animal heart, on the one hand, but was greatly increased in toxicity for living plant protoplasm on the other.

The Effect of Ultraviolet Energy on Erythrocytes in Vitro.—Investigations carried out by MAYER and DWORSKI (*Arch. Phys. Therap., X-ray and Rad.*, 1931, **12**, 709) showed that ultraviolet energy from a Kromayer lamp causes hemolysis of red blood cells. Liberation of pigment from human and guinea pig erythrocytes was accomplished without apparent rupture of the cells. The cytoplasm of the frog's red blood cells disintegrated completely, while the nucleus showed coagulative changes. In the experiments the wave lengths below 300 were responsible for the hemolysis.

Peptic Ulcer of the Esophagus.—A case of peptic ulcer at the lower end of the esophagus is reported by AURELIUS (*Am. J. Roentgenol. and Rad. Therap.*, 1931, **26**, 696). Roentgenologically the ulcer was manifested as a small barium-filled niche. Aurelius considers peptic ulcer of the esophagus a definite disease and of sufficiently frequent occurrence to be of real interest and importance. It has as its cardinal symptoms pain, dysphagia, nausea and vomiting and occasionally hemorrhage and perforation. It has been infrequently diagnosed in the past, but with the development of facilities for Roentgen examination and esophagoscopy, and if sought for in cases of substernal or epigastric pain, its incidence will probably be higher than heretofore. The diagnostic criteria are as yet incomplete and the roentgenologist has an important duty to perform in their further development.

A Review of Pneumonoconiosis.—In a comprehensive article of 58 pages the subject of pneumonoconiosis is reviewed from the standpoint of its etiology, its pathology and its roentgenologic appearances by PANCOAST and PENDERGRASS (*Am. Jour. Roentgenol. and Rad. Ther.*, 1931, **27**, 556). With respect to its etiology the writers again emphasize the overwhelming importance of silica. It is generally conceded that organic dusts either do not produce pneumonoconiosis or their effect is so slight as to be disregarded. Coal is not included among the organic dusts. Workers in coal, asbestos, hard rock (mining, drilling), sand (pulverizing, sandblasting), granite, slate, iron ore, cement and vitreous enamel (painting) are among those liable to pneumonoconiosis in varying degrees. The roentgenologic manifestations also vary somewhat with different dusts. In general the basic roentgenologic characteristics of the three stages of the disease as observed in this country are: First stage: A definite increase in the prominence and extent of the hilum shadows, an increased prominence and thickening of the trunk shadows,

and a greater prominence of the linear markings of the peripheral zone. Second stage: A distinctive distribution of small rounded densities, varying in size from a pinhead to a pea, throughout both lungs. The nodules appear first on the right side, around the root of the lung and are perceptible here before they are seen on the left side; when the distribution becomes general there is no appreciable difference between the two sides. Third stage: This is characterized by diffuse fibrosis and may present any or all of three definite and distinctive appearances: (1) The larger nodules of the second stage, where numerous, may coalesce into large, irregular masses, or be found close together with more or less haze between them; (2) a more or less diffuse fibrosis somewhat similar to the fibrotic process representing the late result of an extensive, bilateral, chronic pulmonary tuberculosis. Usually definite nodules are still present, but not always; (3) massive fibrotic areas having the appearance of extensive pulmonary consolidations. In the late period of the disease there is usually one such area on each side, rather symmetrically located subapically, but sometimes unilateral or more extensive on one side than on the other.

The Bone and Joint Changes of Leprosy.—Bone and joint changes of a remarkable and sometimes spectacular type occur with fair frequency in leprosy. According to CHAMBERLAIN, WAYSON and GARLAND (*Radiology*, 1931, **17**, 950) it is a surprising fact that clinically advanced cases will often show little or no osseous disturbance, while cases with merely mild clinical signs may show marked changes upon Roentgen examination. Cases of the latter type have predominantly nervous lesions in many instances. Bone absorption—a disappearance of bony tissue without antecedent demineralization—is the most constant finding. This varies from slight metaphyseal narrowing to diffuse diaphyseal absorption or "concentric atrophy." Complete disappearance of the bone may occur. The absence of bone production is a conspicuous feature. It is probably that the absorptive changes are not specific but are produced directly through nerve involvement. Bone destruction with rarefaction is a less common finding. When present it is believed to be due to specific leprous osteitis, though secondary pyogenic infection may play a part.

Clinical and Experimental Lead Poisoning: Some Roentgenologic and Anatomic Changes in Growing Bones.—CAFFEY (*Radiology*, 1931, **17**, 957) reports 3 cases of chronic lead poisoning in children, all of which showed changes in the roentgenograms of the long bones. The roentgenologic changes consist of an increase in density of the growing portions of the skeleton, whereas the slow growing and nongrowing portions of the skeleton appear normal. In 2 children who had recovered, a series of transverse lines was observed in the diaphyses and linear rings of density in the ossification centers of the epiphyseal cartilages and the carpal bones, similar to those which have been reported as pathognomonic of healed scurvy.

Roentgenologic Evidence of Chest Tuberculosis in Tuberculin-positive Ambulatory Children.—The material used in this study by STONE and WOLFF (*Radiology*, 1931, **17**, 940) consisted of 93 tuberculin-nega-

tive and 197 tuberculin-positive children who were ambulatory and had no marked symptoms. Forty-two per cent of the tuberculin-positive group had roentgenographic shadows which the writers considered diagnostic. The percentage of such findings was much larger in those cases with the most marked tuberculin reaction. The findings included caseous glands, so enlarged that the resultant tumor projects beyond the vessels, and tuberculous infiltrations in the parenchyma.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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The Neural Symptoms and Signs in Pernicious Anemia.—SMITHBURN and ZERFAS (*Arch. Neurol. and Psychiat.*, 1931, **25**, 1100) report their studies upon 115 cases of pernicious anemia which had been observed for periods varying from 1 to 43 months—the average period of observation being 18½ months. The symptoms and signs referable to the neural system that they observed were: paresthesia, anesthesia, hyperesthesia, impaired sense of vibration, impaired muscle and bone sense (including position), impaired touch, pain and temperature sense, ataxia, altered tendon reflexes, altered cutaneous reflexes, loss of sphincteric control (retention or incontinence), girdle sensations and impaired equilibratory sense, and mental symptoms including depression, irritability, slow thought or speech, hallucinations, illusions, disorientation, ideas of persecution, homicidal tendencies and flight of ideas. Of all the neural symptoms, paresthesia was by far the most common. It was present in 95.6 per cent of the cases. The next in frequency was mental depression, 51.3 per cent; then muscle pains, 42.6 per cent; ataxia, 41.7 per cent; obtuded tendon reflexes, 35.6 per cent; impaired muscle and bone sense, 33.9 per cent; loss of memory, 29.5 per cent; irritability, 27.8 per cent; slow thought or speech, 24.4 per cent; introspection and self pity, 22.6 per cent, exaggerated tendon reflexes, 16.5 per cent; disorientation, 14.7 per cent; joint pains, 13.9 per cent; ideas of persecution, 8.7 per cent; loss of sphincter control, 6.9; per cent illusions or hallucinations, 6 per cent; psychosis, 6 per cent; homicidal tendencies, 2.6 per cent. The patients were all treated with potent fractions of liver except 3, who were given desiccated hog's stomach. All received sufficient amount of this medication to keep their red blood cell level within the normal range with the exception of a comparatively small group upon whom a determination of the maintenance dosage was done. As a result of their observations the authors conclude that: (*a*) Improvement may occur in the neural and psychic changes in patients with pernicious anemia under treatment with adequate amounts of liver extract; (*b*) in some cases arrest of the neural and psychic symptoms, without improvement or retrograde

change, may occur; (*c*) neural and psychic changes may develop for the first time or may steadily progress while the patient is being treated with daily amounts of liver extract adequate to maintain a normal erythrocyte level; (*d*) liver extract does not contain a specific anti-neurotoxic substance.

The Status of Probation.—SHELDON GLUECK (*Mental Hygiene*, 1931, 15, 290) states that probation is an evolution of the common-law method of conditionally suspending a sentence. Its origin for all practical purposes began in August, 1841, with the work of John Augustus, who was the first to undertake the supervision of large numbers of offenders, and who performed such tasks as obtaining employment for them, assisting their families, and the like. Probation grew quickly and spread widely because of a natural human tendency to do the latest thing and to seize upon any new device as a panacea. All through the history of penology this tendency is found at work: first, it was the Pennsylvania congregate and silent system of the penitentiary régime that was soon extensively copied; then, it was the Auburn system of work and recreation in common and isolation at night; then, it was the reformatory panacea of introducing into the régime various measures, such as the grade system, schools, military drill, and the like; then, it was probation and parole that spread so rapidly before their principles could be carefully worked out. Massachusetts was the first state in the world to have recognized the importance of this work by providing for public officials to undertake it. Today, every state except Wyoming has a probation law applying to children; 34 states and the District of Columbia have adult probation; only recently probation was extended to the Federal Courts. In 1927, the number of paid and volunteer probation officers throughout the world was estimated as 20,000; recent reports show that there are over 4000 probation officers in the United States alone. Probation in practice varies all the way from merely "letting the offender off" without more than the usual "supervision" by means of having him report periodically at the probation office, to the most advanced application of modern methods of rehabilitation. In too many places probation work is superficially conducted instead of being "intensively cultivated." Probation work should consist essentially not of "letting the offender off easy" or "giving him another chance," but of taking definite steps to help him avoid misconduct in the future. It is an indisputable fact that in a good many courts in the United States, probation officers are appointed who have not the slightest technical equipment for their tasks. However, the practical experience with life that many an untrained probation officer brings to his job is too valuable to be ignored. What is really needed is a combination of scientific training and maturity of outlook on the problems of life. For the attainment of this the author recommends that the probation offices of a metropolitan district, under the guidance of the board of probation or a similar body, arrange for courses in social case work, psychology and criminology, to be taken by probation officers on two or three afternoons and evenings a week. Future candidates for probation work should be required to have had training in these fields in addition to whatever other pertinent experience they may have. Another outstanding factor in probation work is the inadequacy of

investigations. It is quite obvious that in order to be just to the offender the investigation of the case should be intensive. By "intensive" the author means that the offender himself should be examined psychiatrically, psychologically and physically, and a report on his condition from these points of view should be made; full data with regard to his behavior, his school record, and his industrial career should be secured from appropriate sources; the environmental conditions surrounding him and his family should be ascertained; an estimate of the probable etiologic factors in the case should be made and recorded; and on the basis of these findings and of interviews with the dependent, a plan of treatment should be worked out. The plan should be definitely regarded as tentative, and should be modified from time to time in the light of the results. The supervisory work should consist of frequent visits to the family and the focusing of the community's educational, vocational and social resources on the problems presented by the probationer and his family, and not the mere occasional reporting of the probationer at the office to have his name checked off. Record keeping is an important part of the work of probation. Many probation offices in this country cannot tell how many probationers they have at any one time; there are offices in which records of the number of investigations are not kept separately from records of the number of supervisions. There are few offices that publish an annual report. A research unit in every large probation office is necessary—is indispensable in regulating the work and growth and "personality" of this office. The author further points out that criminal law is a stepchild of the law schools—taught today much the same as it was 50 years ago—by the youngest, least experienced teacher; that it is usually taught 2 hours a week instead of 3, and for only one semester instead of two. In the courts the least experienced or weakest judge is usually assigned to criminal cases—or a judge behind in his civil business is allowed to catch up by an assignment to the criminal branch. Criminalistics must be raised to a plane of dignity in the curricula of the law schools. Students interested in criminals should be given more time to study criminal law. And judges should be specialized in criminal work, for this administration of criminal justice is a fulltime, man-sized job. It should not be made a "stop-gap" or "side line."

A General Symptom in Brain Tumor.—KLIMKE (*München. med. Wchnschr.*, 1931, **77**, 50) presents 4 cases of cerebral tumor in which Kehrer's two signs were demonstrable in unmistakable fashion. The first of these comprises the production of pain on deep pressure over the back of the neck a little to one side of the midline, at the site of emergence of the great occipital nerve. Associated pain reactions consist in flushing of the face, and flexion of the head and neck backward and to the homolateral side. Kehrer's other sign consists of pain on deep pressure over the points of emergence of the three branches of the trigeminal nerve on the face. While this maneuver may cause pain on one side only or perhaps merely in one or two of the branches in cases of tic douloureux and of migraine, in patients with cerebral tumor all six points are painful on pressure. The author believes that these are early and valuable signs of increased intracranial tension analogous to

the demonstration of papilledema. He states that further research is required to determine which of the two signs can be illicited first and whether there is any correlation between priority of appearance and site of the neoplasm.

Pain Pathways in the Sympathetic Nervous System.—MIXTER and WHITE (*Arch. Neurol. and Psychiat.*, 1931 **15**, 986) present clinical evidence suggesting that sensory impulses may pass over pathways running in or intimately associated with the ganglia of the sympathetic chain and the white rami. They remark that the conception that sensory impulses are carried only by the cranial and spinal nerves has been held and taught for many years—that such a conception is hard to disprove. The conception of the anatomy of the sensory pathways in the sympathetic system to which they adhere is as follows: Pain-bearing nerve fibers probably run in many of the sympathetic nerves that course along the bloodvessels of the head and neck. Whether these fibers are connected with the sympathetic ganglia of the head they do not know, but believe that it is possible. They do not believe that any of these fibers enter the central nervous system above the first white rami above this level, and suggest that they may enter as low as the second and third. Pain pathways from the arm may enter through the sympathetic rami as low as the third and fourth dorsal. They think that pain from the aortic arch and the heart enters the spinal cord from the upper five or six dorsal sympathetic ganglia, and that it may reach the ganglia by two different routes: (1) One route is over the middle and inferior cardiac nerves to the cervical sympathetic trunk. As there are no white rami joining the cervical sympathetic with the cord, the pain fibers must descend at least to the first dorsal segment before they can enter the central nervous system. (2) A second set of gray rami runs from the posterior cardiac and pulmonary flexures directly across the posterior mediastinum to the second, third, fourth and sometimes to the fifth and sixth ganglia. They also believe that from the course of the splanchnic nerves, pain from the upper abdominal viscera enters the cord in the dorsal region, probably from the fifth dorsal to the first lumbar sympathetic ganglia. The technique used was: As a diagnostic measure they injected procain hydrochlorid into the ganglia believed to play a part in the picture. If the result seemed satisfactory, the ganglia were removed, or alcohol was injected into them, or the communicant rami were severed. Cases presented were: Two cases of atypical neuralgias of the face in which a complete removal of the cervicodorsal and second dorsal ganglia was done in 1 case with complete relief, cervicodorsal and the second dorsal ganglia in the second case with only partial relief; 1 case of causalgia of the hand in which the two upper dorsal ganglia were removed with complete relief; 1 case of syphilitic aneurysm of the aortic arch with radiating pain, alcohol was injected into the first and second communicant rami with complete relief; 19 cases of angina pectoris in which the dorsal ganglia were injected with alcohol and 4 in which dorsal ganglionectomy was performed with satisfactory results; 1 case of thoracic and gastric crises of tabes dorsalis in which the seventh to ninth ganglia were removed, the great splanchnic nerve was severed and the fourth

to the seventh rami cut with complete relief of pain. The results which the authors obtained in these cases have caused them to conclude that these patients suffering from the severest types of pain were relieved by interruption of the dorsal sympathetic fibers, and, that there may be definite sensory pathways running in the dorsal sympathetic chain.

PATHOLOGY AND BACTERIOLOGY

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Pneumococcus Vaccine Introduced in the Upper Respiratory Tract.—Animal experiments reported by STUPPY, CANNON and FALK (*J. Prev. Med.*, 1930, **5**, 97) have shown that the daily insufflation of heat killed suspensions of pneumococci of Types I and II into the nose and throat of rabbits produces active immunity. There was no protection after intraperitoneal injections of living, virulent pneumococci against any bacteria other than those of the type used to immunize the animal. Following vaccination by this method the intratracheal insufflation of living, virulent pneumococci produced a changed type of tissue reaction in the lungs of the animal in which the macrophage was the predominant cell, accompanied by a considerable number of eosinophils, in contrast to the usual polymorphonuclear reaction. This was interpretated as being evidence of a definite type of tissue immunity, which was, however, only relative, since heterologous cultures of living pneumococci produced the same type of local immune reaction but to a lesser degree. Acid killed suspensions of pneumococci were fed orally to humans by Ross (*Proceed. Soc. Exper. Biol. and Med.*, 1931, **28**, 822) and their serum tested for antibody content by its ability to protect mice injected with fatal doses of pneumococcus culture. In the serum of a number of the subjects there was clear evidence of an increase of antibody content. In some the result was in doubt, while in others no effect could be detected. The absence of demonstrable antibodies in the serum, however, may not mean the lack of an increased resistance to the microörganism since animal experiments seem to indicate that, in some individuals active immunity may be produced without their development.

A Cytopathologic Study of Acute and Chronic Morphinism in the Albino Rat.—Studies on acute and chronic morphinism in the albino rat were undertaken by WEN-CHAO MA (*Chinese J. Physiol.*, 1931, **5**, 251). In acute morphinism in animals which had received a single large dose, the injection of the drug is followed by a period of stimulation lasting from 1 to 5 hours. Cytopathologic examination of muscular, nervous and epithelial tissues revealed that the Golgi lipoid, which the

author regards as a special material dissociated from the mitochondria, has become greatly increased in amount, while the mitochondria themselves remain in a normal condition. The initial stimulating effects of the drug are followed by a period of depression (6 to 11 hours after the last injection) in which the Golgi lipoid becomes greatly decreased while the mitochondria are slightly increased. Chronic morphinism was produced by daily administration of this drug, over a period of 8 months. In the "craving periods" (2 to 3 days after the last injection) the lipoid is greatly decreased while the mitochondria are moderately increased. When the craving is satisfied with an injection of morphin the lipoid is found to be moderately increased while the mitochondria maintain their normal appearance. As the animal again passes into the craving period, the lipoid gradually decreases. When the animal receives regular administrations of morphin, no deviation from the normal is found. When no more morphin is given, however, the Golgi lipoid almost disappears and the rat becomes very inactive. If, however, animals from which morphin had been withheld were fed on lecithin, neither the Golgi lipoid nor the animal's activity was reduced. The author suggests that the result of this study may possibly form a basis for a rational method of treatment in human morphin addiction.

HYGIENE AND PUBLIC HEALTH

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Mechanism of Natural Immunity to Diphtheria. Preliminary Report of Experiments in Puerto Rico.—The extensive studies of specific immunity to diphtheria which have been made in the last 30 years, especially since the development of the Schick test, have shown that antitoxic immunity is related in a very regular way to age. Diphtheria antitoxin sufficient to give a negative Schick test is present, at birth, in the blood of babies born of Schick-negative mothers; but this immunity, which is shown to be passively received from the mother, is gradually lost, so that, before the end of the first year of life, the great majority of infants have become Schick-positive. Thereafter the proportion of Schick-negatives increases steadily with each year of age until, at adolescence, 70 to 90 per cent show this evidence of immunity. The study reported by GARRIDO-MORALES and MANDRY (*Am. J. Hyg.*, 1931, **14**, 89) was planned to test, by direct observation, the theory that the change from Schick-positive to Schick negative is mainly due to subclinical infection, and at the same time to give more exact information on the prevalence of carrier infections by means of observations repeated

at short intervals. It will perhaps add to the interest of the results that they refer to a tropical country, where clinical diphtheria is relatively rare. The paper includes only the results obtained during the first 3 months of a study which is being continued. The authors found that Schick tests of 642 children attending one of the larger public schools in San Juan, Porto Rico, showed higher proportions of Schick-negatives than usually have been found at corresponding ages in New York, Baltimore and other cities in the northern United States. This accords with previous observations in the Tropics. Bacteriologic examinations made at the time of the first Schick tests (March, 1930) showed 1.4 per cent of the children to be carriers of virulent and 5.8 per cent to be carriers of avirulent diphtheria bacilli. Carrier infections, both with virulent and with avirulent organisms, were somewhat more frequent in Schick-positive than in Schick-negative children. Bacteriologic examinations of 194 originally Schick-positive children, repeated weekly for a period of 3 months discovered a total of 26 (13.4 per cent) carriers of virulent and 42 (21.6 per cent) carriers of avirulent diphtheria bacilli. All those found carrying virulent organisms were previously or later found harboring avirulent bacilli. During the 3 months of observation, negative Schick reactions developed in 85 per cent (22 of 26) of the demonstrated virulent carriers, in 12 per cent of those found carrying only avirulent organisms, and in 9.5 per cent of those showing no positive cultures. Of the four demonstrated carriers of virulent organisms who remained Schick-positive at the end of June, two showed negative, and two positive reactions, when retested the following September. Twenty of the 22 known carriers of virulent bacilli who had developed negative Schick reactions before June 30, were retested 3 to 5 months later. Sixteen of the 20 (80 per cent) were found still Schick-negative, while the remainder showed positive reactions. The completeness and durability of the negative Schick reaction developing after demonstrated infection with organisms classed as virulent showed some relation to the degree of toxicity of the cultures.

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